A. INGREDIENT NAME:

HYDRAZINE SULFATE

B. Chemical Name:

Hydrazinium Sulfate, Hydrazonium Sulfate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay:	99.0% min.	99.3%

E. Information about how the ingredient is supplied:

White Crystalline Powder

F. Information about recognition of the substance in foreign pharmacopeias:

USP 23, Indian Pharmacopeia 3rd Ed.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Gold, J. Use of Hydrazine Sulfate in terminal and Preterminal Cancer patients: results of investigational new drug (IND) study in 84 valuable patients. *Oncology.* 1975; 32(1): 1-10

Chlebowski, R. T., Bulcavage, L., and Grosvenor, M. Hydrazine Sulfate in Cancer patients with weight loss. A placebo-controlled clinical experience. *Cancer.* 1987; 59(3): 406-410.

Bairam, A. Theophylline versus caffeine: comparative effects in treatment of idiopathic apnea in the preterm infant. *J. Pediatr.* 1987; 110:636.

Eisenberg, M. G. and Kang, N. Stability of citrated caffeine solutions for injectable and external use. *Am. J. Hosp. Pharm.* 1984;41:2405.

H. Information about dosage forms used:

I. Information about strength:

60mg, 3 times/d

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 254°
Oxidizing Agents
Bases

L. Formulations:

M. Miscellaneous Information:

50-1876
49320

CERTIFICATE OF ANALYSIS

PRODUCT: HYDRAZINE SULFATE REAGENT
RELEASE #: N
LOT # :L609141
GRADE: A.C.S.
CODE:G61024

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	WHITE CRYSTALLINE POWDER E	CONFORMS
2.	Identification	To pass test	Passes test
3.	Residue on Ignition	0.05% max.	0.01%
4.	Insoluble matter	0.005% max.	0.0025%
5.	Assay	99.0% min.	99.3% D
6.	Heavy Metals	0.002% max.	< 0.001%
7.	Chloride	0.005% max.	0.002%
8.	Iron	0.001% max.	< 0.0003%

ATTENTION: TONY HATCHETT

Date :04/09/97
10690

Prepared by : A. HAZARI

Approved by : 4/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: HYDRAZINE SULFATE A.C.S.REAGENT

MANUFACTURE LOT NO.: 609141

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE TO ORTHORHOMBIC CRYSTALS.GLASS-LIKE PLATES OR PRISMS.

2) SOLUBILITY.:
SOLUBLE IN ABOUT 33 PARTS OF COLD WATER;FREELY SOLUBLE IN HOT WATER.INSOLUBLE IN ALCOHOL.

3) MELTING POINT.:
MELTS AT ABOUT 254 degree. K

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A)A SOLUTION RESPONDS TO THE TESTS FOR SULFATE.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

Use your web browser's "Back" key to return to previous topic.

Hydrazine Sulfate

****** MATERIAL SAFETY DATA SHEET ******

Hydrazine Sulfate
11070

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Hydrazine Sulfate
Catalog Numbers:
H320 500, H320-500, H320500
Synonyms:
Diamine Sulfate; Hydrazine Monosulfate; Hydrazinium Sulfate.
Company Identification: Fisher Scientific
1 Reagent Lane
Fairlawn, NJ 07410
For information, call: 201-796-7100
Emergency Number: 201-796-7100
For CHEMTREC assistance, call: 800-424-9300
For International CHEMTREC assistance, call: 703-527-3887

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
10034-93-2	HYDRAZINE SULFATE	>99	233-110-4

Hazard Symbols: T
Risk Phrases: 23/24/25 43 45

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: white.
Danger! Corrosive. Carcinogen. May be harmful if swallowed. Sensitizer. May cause lung damage. May cause severe eye irritation and possible injury. May cause liver and kidney damage. May cause severe skin irritation and possible burns. May cause severe respiratory and digestive tract irritation with possible burns. May cause cancer based on animal studies. Material is shock sensitive and potentially explosive.
Target Organs: Blood, kidneys, central nervous system, liver.

Potential Health Effects
Eye:
Contact with eyes may cause severe irritation, and possible eye burns. May cause eye injury.
Skin:
May cause skin sensitization, an allergic reaction, which becomes

evident upon re-exposure to this material. May cause severe skin irritation with possible burns, especially if skin is wet or moist.

Ingestion:
May cause liver and kidney damage. May cause severe digestive tract irritation with abdominal pain, nausea, vomiting and diarrhea. May cause corrosion and permanent tissue destruction of the esophagus and digestive tract. Exposure may cause anemia and other blood abnormalities. May be harmful if swallowed.

Inhalation:
Irritation may lead to chemical pneumonitis and pulmonary edema. May cause liver and kidney damage. May cause severe irritation of the upper respiratory tract with pain, burns, and inflammation. May cause effects similar to those described for ingestion.

Chronic:
Prolonged or repeated skin contact may cause sensitization dermatitis and possible destruction and/or ulceration. May cause liver and kidney damage. May cause cancer according to animal studies. May cause digestive tract disturbances.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.

Skin:
Get medical aid immediately. Immediately flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:
Do NOT induce vomiting. If victim is conscious and alert, give 2-4 cupfuls of milk or water. Get medical aid immediately.

Inhalation:
Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:
Treat symptomatically and supportively.

Antidote:
No specific antidote exists.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Dusts at sufficient concentrations can form explosive mixtures with air. Combustion generates toxic fumes. Material is shock sensitive and potentially explosive. Greatly increases the burning rate of combustible materials. Violently decomposes when heated under confinement.

Extinguishing Media:
For small fires, use water spray, dry chemical, carbon dioxide or chemical foam.

Autoignition Temperature: Not applicable.
Flash Point: Not applicable.
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:
Sweep up, then place into a suitable container for disposal. Avoid generating dusty conditions.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Wash thoroughly after handling. Remove contaminated clothing and

wash before reuse. Use with adequate ventilation. Minimize dust generation and accumulation. May form flammable dust-air mixtures. Loosen closure cautiously before opening. Do not get on skin and clothing. Empty containers retain product residue, (liquid and/or vapor), and can be dangerous. Do not ingest or inhale. Avoid mechanical shock and friction. Do not pressurize, cut, weld, braze, solder, drill, grind, or expose empty containers to heat, sparks or open flames.

Storage:

Keep away from heat, sparks, and flame. Do not store near combustible materials. Store in a tightly closed container. Store in a cool, dry, well-ventilated area away from incompatible substances.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:

Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
HYDRAZINE SULFATE	none listed	none listed	none listed

OSHA Vacated PELs:

HYDRAZINE SULFATE:

No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:

Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:

Wear appropriate protective gloves to prevent skin exposure.

Clothing:

Wear appropriate protective clothing to prevent skin exposure.

Respirators:

Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Solid
Appearance:	white
Odor:	None reported.
pH:	1.3 (0.2M solution)
Vapor Pressure:	Negligible.
Vapor Density:	Not applicable.
Evaporation Rate:	Negligible.
Viscosity:	Not available.
Boiling Point:	Not available.
Freezing/Melting Point:	489 deg F
Decomposition Temperature:	Not available.
Solubility:	Soluble in water.
Specific Gravity/Density:	1.4 (water=1)
Molecular Formula:	H4N2.H2SO4
Molecular Weight:	130.12

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:

Stable under normal temperatures and pressures. Substance is shock sensitive and thermally unstable.

Conditions to Avoid:

Mechanical shock, incompatible materials, temperatures above 160°C.

Incompatibilities with Other Materials:
Oxidizing agents, combustible materials, sodium amide.
Hazardous Decomposition Products:
Nitrogen oxides, carbon monoxide, oxides of sulfur, carbon dioxide.
Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 10034-93-2: MV9625000
LD50/LC50:
CAS# 10034-93-2: Oral, mouse: LD50 = 740 mg/kg; Oral, rat: LD50 = 601 mg/kg.
Carcinogenicity:
HYDRAZINE SULFATE -
California: carcinogen
NTP: Suspect carcinogen
OSHA: Possible Select carcinogen
Epidemiology:
Oral and intraperitoneal administration of hydrazine salts t o animals have produced lung and liver carcinomas.
Teratogenicity:
No information available.
Reproductive Effects:
No information available.
Neurotoxicity:
No information available.
Mutagenicity:
Please refer to RTECS# MV9625000 for specific information.
Other Studies:
Skin irritation, guinea pig: slight. Eye irritation, rabbit: severe.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
No information available.
Environmental Fate:
No information reported.
Physical/Chemical:
No information available.
Other:
None.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.
RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
Shipping Name: CORROSIVE SOLID,ACIDIC,INORGANIC,N.O.S. (HYDRAZINE SULFATE)
Hazard Class: 8
UN Number: UN3260
Packing Group: II
IMO
No information available.
IATA
No information available.
RID/ADR
No information available.
Canadian TDG
Shipping Name: CORROSIVE SOLIDS NOS (HYDRAZINE SULFATE)
Hazard Class: 8(9.2)
UN Number: UN1759

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 10034-93-2 is listed on the TSCA inventory.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

SARA Codes

CAS # 10034-93-2: acute, chronic, reactive.

Section 313

This material contains HYDRAZINE SULFATE (CAS# 10034-93-2, >99%),which is subject to the reporting requirements of Section 313 of SARA Title III and 40 CFR Part 373.

Clean Air Act:

This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

HYDRAZINE SULFATE can be found on the following state right to know lists: New Jersey, Florida, Pennsylvania, Minnesota, Massachusetts.
The following statement(s) is(are) made in order to comply with the California Safe Drinking Water Act:
WARNING: This product contains HYDRAZINE SULFATE, a chemical known to the state of California to cause cancer.
California No Significant Risk Level:
CAS# 10034-93-2: no significant risk level = 0.2 ug/day

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: T

Risk Phrases:

R 23/24/25 Toxic by inhalation, in contact with skin and if swallowed.
R 43 May cause sensitization by skin contact.
R 45 May cause cancer.

Safety Phrases:

S 44 If you feel unwell, seek medical advice (show the label where possible).
S 53 Avoid exposure - obtain special instructions before use.

WGK (Water Danger/Protection)

CAS# 10034-93-2:

Canada

CAS# 10034-93-2 is listed on Canada's DSL/NDSL List.
This product has a WHMIS classification of D2A, E.
CAS# 10034-93-2 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 9/22/1995 Revision #3 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Spectral purity—Measure in a 1-cm cell at 300 nm, with a suitable spectrophotometer, against air as the blank: its absorbance is not more than 0.08.

Hexanes (suitable for use in ultraviolet spectrophotometry); usually a mixture of several isomers of hexane (C_6H_{14}), predominantly *n*-hexane, and methylcyclopentane (C_6H_{12})—Use ACS reagent grade.

Hexanitrodiphenylamine (*Dipicrylamine*), $C_{12}H_5N_7O_{12}$—**439.21**—Yellow-gold powder or prisms. *Explosive.* Usually contains about 15% of water as a safety precaution. Insoluble in water, in alcohol, in acetone, and in ether; soluble in glacial acetic acid and in alkalies.

Water, Method I ⟨921⟩: not more than 16%.

Hexanophenone, $C_{12}H_{16}O$—**176.26**—Yellow liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 30-m × 0.25-mm capillary column coated with a 1-μm layer of phase G3; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{12}H_{16}O$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: 1.511 ± 0.002 at 20°.

Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension—Use a suitable grade.[1]

Suitability—When used in the assay of lactulose, determine that a suitable absorbance-versus-concentration slope is obtained, using USP Lactulose RS, the reagent blank absorbance being not more than 0.020.

Histamine Dihydrochloride, $C_5H_9N_3 \cdot 2HCl$—**184.07**—Use USP Histamine Dihydrochloride RS.

Hydrazine Hydrate, 85% in Water, $(NH_2)_2 \cdot H_2O$—**50.06**—Colorless liquid.

Assay—Transfer 600 mg, accurately weighed, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Pipet 10 mL into a suitable beaker, add 1.0 g of sodium bicarbonate and 50.0 mL of 0.1 *N* iodine VS. Titrate the excess iodine with 0.1 *N* sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* iodine is equivalent to 12.52 mg of $(NH_2)_2 \cdot H_2O$. Not less than 83% is found.

Hydrazine Dihydrochloride, $(NH_2)_2 \cdot 2HCl$—**104.97**—White powder.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of water. Add carefully while stirring, 1 g of sodium bicarbonate. [*Caution—There may be a rapid evolution of carbon dioxide.*] Titrate with 0.1 *N* iodine solution, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 *N* iodine solution is equivalent to 2.63 mg of $(NH_2)_2 \cdot 2HCl$. Not less than 98% is found.

Hydrazine Sulfate, $(NH_2)_2 \cdot H_2SO_4$—**130.13**—Use ACS reagent grade.

Hydriodic Acid, HI—**127.91**—Use ACS reagent grade (containing not less than 47.0% of HI).

NOTE—For *Methoxy Determination* ⟨431⟩, use hydriodic acid that is labeled "for alkoxyl determination," or that is purified as directed under *Methoxy Determination* ⟨431⟩. Use this grade also for alkoxyl determinations in assays in the individual monographs.

Hydrochloric Acid, HCl—**36.46**—Use ACS reagent grade.

Hydrochloric Acid, Diluted (10 percent)—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

Hydrofluoric Acid, HF—**20.01**—Use ACS reagent grade.

Hydrogen Peroxide, 30 Percent, H_2O_2—**34.01**—Use ACS reagent grade.

Hydrogen Peroxide Solution—Use *Hydrogen Peroxide Topical Solution.*

Hydrogen Sulfide, H_2S—**34.08**—Colorless, poisonous gas, heavier than air. Soluble in water. Is generated by treating ferrous sulfide with diluted sulfuric or diluted hydrochloric acid. Other sulfides yielding hydrogen sulfide with diluted acids may be used. Is also available in compressed form in cylinders.

Hydrogen Sulfide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator, the latter consisting of a suitable lead salt.

NOTE—A suitable detector tube that conforms to the monograph specification is available from National Draeger, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 67 19001, Measuring Range 1 to 20 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices.*

Hydroquinone, $C_6H_4(OH)_2$—**110.11**—Fine, colorless or white, needle crystals. Darkens on exposure to air and light. Soluble in water, in alcohol, and in ether.

Assay—Weigh accurately about 250 mg, and dissolve in a mixture of 100 mL of water and 10 mL of 0.1 *N* sulfuric acid in a 250-mL conical flask. Add 3 drops of a 1 in 100 solution of diphenylamine in sulfuric acid, and titrate with 0.1 *N* ceric sulfate VS until the solution is red-violet in color. Each mL of 0.1 *N* ceric sulfate is equivalent to 5.506 mg of $C_6H_4(OH)_2$. Not less than 99% is found.

Melting range ⟨741⟩: between 172° and 174°.

3′-Hydroxyacetophenone, $C_8H_8O_2$—**136.15**—Light brown powder chips and chunks. Melts at about 96°. Sparingly soluble in chloroform, yielding a clear, light yellow solution.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G1; the detector and the injection port temperature are maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280° and held at that temperature for 10 minutes. The area of the main peak is not less than 97% of the total peak area.

4′-Hydroxyacetophenone, $HOC_6H_4COCH_3$—**136.15**—Gray powder, melting at about 109°.

***p*-Hydroxybenzoic Acid,** $C_7H_6O_3$—**138.12**—White crystals.

Assay—Transfer about 700 mg, accurately weighed, to a suitable container, and dissolve in 50 mL of acetone. Add 100 mL of water, mix, and titrate with 0.5 *N* sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 *N* sodium hydroxide is equivalent to 69.06 mg of $C_7H_6O_3$: not less than 97% is found.

Melting range ⟨741⟩: over a range of 2° that includes 216°.

4-Hydroxybenzoic Acid Isopropyl Ester, $HOC_6H_4COOCH(CH_3)_2$—**180.20**—Use a suitable grade.[32]

Melting range ⟨741⟩: between 84° and 87°.

1-Hydroxybenzotriazole Hydrate, $C_6H_5N_3O \cdot xH_2O$—**135.13** (anhydrous)—White crystalline powder. Sparingly soluble in alcohol yielding a clear, pale yellow solution.

2-Hydroxybenzyl Alcohol, $C_7H_8O_2$—**124.14**—Off-white flakes. Very soluble in alcohol, in chloroform, and in ether; soluble in 15 parts water and in benzene.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩), equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-μm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_7H_8O_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 83° and 85°.

4-Hydroxyisophthalic Acid, $C_8H_6O_4$—**182.13**—Colorless branched needles. Freely soluble in alcohol and in ether.

Melting range ⟨741⟩: between 314° and 315°, with decomposition.

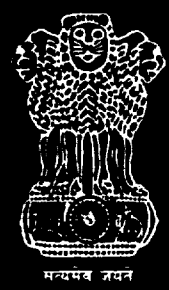
Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume – II
(Q – Z & Appendices)

Third Edition



PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

A fraction from petroleum containing about 90 per cent of *n*-hexane.

DESCRIPTION – Colourless, mobile, highly flammable liquid.

DISTILLATION RANGE – Not less than 95 per cent, distils between 67° and 70°, Appendix 5.3.

WT. PER ML – At 20°, 0.670 to 0.677 g, Appendix 5.19.

NON-VOLATILE MATTER – When evaporated on a water-bath and dried to constant weight at 105°, leaves not more than 0.01 per cent w/v of residue.

Histamine Acid Phosphate

Of the Indian Pharmacopoeia.

Histamine Dihydrochloride : $C_5H_9N_3,2HCl = 184.07$

DESCRIPTION – White crystalline powder.

SOLUBILITY – Freely soluble in *water* and in *methyl alcohol*; soluble in *alcohol*.

MELTING POINT – About 250°, Appendix 5.11.

DL-Histidine Monohydrochloride

$N:CH.NH.CH:C.CH_2.CH(NH_2).COOH,HCl = 191.62$

Contains not less than 99.0 per cent of $C_6H_9N_3O_2,HCl$, calculated with reference to the substance dried to constant weight at 105°.

DESCRIPTION – White, crystalline powder.

SOLUBILITY – Soluble in *water*.

LOSS ON DRYING – Loses not more than 9.0 per cent of its weight, when dried to constant weight at 105°, Appendix 5.8.

SULPHATED ASH – Not more than 0.1 per cent, Appendix 3.2.7.

ASSAY – Carry out the method for the *determination of nitrogen, Method A*, Appendix 3.3.5, using 0.15 g and 7 ml of *nitrogen-free sulphuric acid*. Each ml of *0.1N sulphuric acid* is equivalent to 0.00639 g of $C_6H_9N_3O_2,HCl$.

Holmium Oxide : $Ho_2O_3 = 377.86$

DESCRIPTION – A yellow solid.

SOLUBILITY – Practically insoluble in *water*.

Holmium Perchlorate Solution

A 5 per cent w/v solution of *holmium oxide* in *1.4 M perchloric acid*.

Hydrazine Hydrate : $NH_2.NH_2,H_2O = 50.06$

DESCRIPTION – Clear, colourless liquid with an ammoniacal odour.

SOLUBILITY – Miscible with *water*.

WT. PER ML – 1.03 g, Appendix 5.19.

Hydrazine Sulphate : $NH_2.NH_2,H_2SO_4 = 130.12$

Contains not less than 99.0 per cent of $N_2H_6SO_4$.

DESCRIPTION – White, crystalline powder.

SOLUBILITY – Freely soluble in *water*; practically insoluble in *alcohol*.

MELTING POINT – About 254°, Appendix 5.11.

CHLORIDE – 1 g complies with the *limit test for chlorides*, Appendix 3.2.2.

IRON – 1 g complies with the *limit test for iron*, Appendix 3.2.5.

SULPHATED ASH – Not more than 0.05 per cent, Appendix 3.2.7.

ASSAY – Weigh accurately about 0.1 g and dissolve in 20 ml of *water*. Add 3 g of *sodium bicarbonate* and titrate with *0.1N iodine*, using *starch solution* as indicator. Each ml of *0.1N iodine* is equivalent to 0.003253 g of $N_2H_6SO_4$.

Hydriodic Acid : HI = 127.91

Constant-boiling hydriodic acid contains 55.0 per cent w/w of HI (limits, 54.0 to 56.0).

DESCRIPTION – Almost colourless liquid when freshly made, but rapidly becoming yellow to brown owing to the liberation of iodine.

SOLUBILITY – Miscible in all proportions with *water* and with *alcohol*.

BOILING POINT – About 127°, Appendix 5.3.

WT. PER ML – At 20°, about 1.7 g, Appendix 5.19.

CHLORIDE AND BROMIDE – To 0.2 ml add 15 ml of *water*, 50 mg of *sodium sulphate*, 5 ml of *dilute ammonia solution* and 20 ml of *0.1N silver nitrate*, shake and filter; to the filtrate add 10 ml of *dilute nitric acid*. The opalescence produced is not greater than the standard opalescence obtained in the *limit test for chlorides*, Appendix 3.2.2.

SULPHATE – Dilute 1 ml with 50 ml of *water* and add 1 ml of *barium chloride solution*. The turbidity produced should not be greater than the standard opalescence obtained in the *limit test for sulphates*, Appendix 3.2.8.

NON-VOLATILE MATTER – When evaporated on a water-bath, and dried to constant weight at 105°, leaves not more than 0.5 per cent w/w of residue.

ASSAY – Weigh accurately about 0.6 g into a stoppered flask containing about 10 ml of *water*, dilute with 25 ml of *water* and titrate the free iodine with *0.1N sodium thio-*

TABLE 2

Size No.	Kinematic Viscosity Range (Centistokes)	Volume Bulb C (ml) (±5%)	Inside Diameter of Tube N (mm)	Inside Diameter of Tube R (mm) (±2%)
1	3.5* to 10	0.64	5.6	2.8 to 3.2
1A	5 to 30	0.84	5.6	2.8 to 3.2
2	20 to 100	1.15	5.6	2.8 to 3.2
2A	60 to 300	1.51	5.6	2.8 to 3.2
3	200 to 1100	2.06	5.6	3.7 to 4.3
3A	600 to 3000	2.74	5.6	4.6 to 5.4
4	2000 to 10,000	3.70	5.6	4.6 to 5.4
4A	6000 to 30,000	4.97	5.6	5.6 to 6.4
5	20,000 to 100,000	6.76	5.6	6.8 to 7.5

*350 minimum flow time; 200 minimum flow time for all other sizes

any time while the flow time is being measured, the determination must be repeated.

Calculate the kinematic viscosity in centistokes (V) from the equation:

$$v = Ct.$$

where

t = time in seconds for the meniscus to fall from E to F

C = the constant of the viscometer, determined by observations on a liquid of known viscosity.

Method C : (Using the Rotating Viscometer)

The rotating viscometer measures the shearing forces in a liquid medium placed between two coaxial cylinders one of which is driven by a motor and the other is caused to revolve by the rotation of the first. Under these conditions, the viscosity becomes a measurement of the angle of deflection of the cylinder caused to revolve, expressed in newton metres.

Method—Operate the Rotating Viscometer in accordance with the manufacturer's instructions and carry out the determination of viscosity of the liquid being examined, at the temperature and angular velocity or shear rate specified in the individual monograph.

Calculate the dynamic viscosity (n) in centipoises.

5.19 WEIGHT PER MILLILITRE AND SPECIFIC GRAVITY

Weight per Millilitre

The weight per millilitre of a liquid is the weight in g of 1 ml of a liquid when weighed in air at 25°, unless otherwise specified.

Method : Select a thoroughly clean and dry pycnometer. Calibrate the pycnometer by filling it with recently boiled and cooled *water* at 25° and weighing the contents. Assuming that the weight of 1 ml of *water* at 25° when weighed in air of density 0.0012 g per ml, is 0.99602 g, calculate the capacity of the pycnometer. (Ordinary deviations in the density of air from the value given do not affect the result of a determination significantly). Adjust the temperature of the substance to be examined, to about 20° and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25°, remove any excess of the substance and weigh. Subtract the tare weight of the pycnometer from the filled weight of the pycnometer. Determine the weight per millilitre by dividing the weight in air, expressed in g, of the quantity of liquid which fills the pycnometer at the specified temperature, by the capacity expressed in ml, of the pycnometer at the same temperature.

Specific Gravity

The specific gravity of a liquid is the weight of a given volume of the liquid at 25° (unless otherwise specified) compared with the weight of an equal volume of *water* at the same temperature, all weighings being taken in air.

Method : Proceed as described under **Wt. per ml.** Obtain the specific gravity of the liquid by dividing the weight of the liquid contained in the pycnometer by the weight of *water* contained, both determined at 25° unless otherwise directed in the individual monograph.

12831-c

Hydrazine Sulphate.

$H_6N_2O_4S = 130.1$

CAS — 302-01-2 (hydrazine); 10034-93-2 (sulphate).

Crystals. **Soluble** 1 in about 33 of water, freely soluble in hot water; practically **insoluble** in alcohol. A 0.2M solution in water has a pH of 1.3.

Hydrazine sulphate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinic chloride for corneal tattooing (see Chloroplatinic Acid, p.1693).

An account of the successful treatment of industrial hydrazine poisoning with pyridoxine.— J. K. Kirklin *et al.*, *New Engl. J. Med.*, 1976, *294*, 938.

A report of fatal choroidal melanoma in a worker who had been exposed to hydrazine for 6 years.— D. M. Albert and C. A. Puliafito (letter), *New Engl. J. Med.*, 1977, *296*, 634.

The use of hydrazine sulphate by a laboratory worker was associated with the development of a syndrome similar to systemic lupus erythematosus — P. J. Durant and R. A. Harris (letter), *New Engl. J. Med.*, 1980, *303*, 584.

A discussion of hydrazine sulphate as an antineoplastic agent.— W. Regelson, *J. Am. med. Ass.*, 1980, *243*, 337.

12832-k

Hydrogen Sulphide. Sulphuretted Hydrogen.

$H_2S = 34.08$.

CAS — 7783-06-4.

A colourless inflammable gas with a characteristic odour; the intensity of the smell gives no indication of concentration.

Adverse Effects. Hydrogen sulphide poisoning is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein; concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. Pulmonary irritation, edema, and respiratory failure usually occur after acute poisoning; prolonged exposure to low concentrations may give rise to severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, rhinitis, bronchitis, stomatitis, pharyngitis, digestive disturbances, headache, lassitude, and skin rashes. There are some similarities to poisoning with cyanides.

A discussion of poisoning by hydrogen sulphide.— *Lancet*, 1978, *1*, 28. Comments.— A. Downie (letter), *ibid.*, 219; C. H. B. Binns (letter), *ibid.*, 501; A. Downie (letter), *ibid.*

Concentrations of about 200 ppm caused irritation of the respiratory tract and, on prolonged exposure, pulmonary oedema. Toxicity to the CNS could occur suddenly at concentrations in excess of 500 ppm and immediate death might follow concentrations in excess of 1000 ppm. Irritation to the eyes occurred at concentrations of less than 50 ppm.— *Methods for the Detection of Toxic Substances in Air, Hydrogen Sulphide*, London, HM Stationery Office, 1969.

Further references: W. W. Burnett *et al.*, *Can. med. Ass. J.*, 1977, *117*, 1277; R. P. Smith (letter), *ibid.*, 1978, *118*, 775; W. W. Burnett and E. G. King (letter), *ibid.*, 776; *J. Am. med. Ass.*, 1978, *239*, 1374.

Treatment of Adverse Effects. After exposure to hydrogen sulphide place the patient in fresh air, give inhalations of oxygen and, if necessary, assist the respiration. Antibiotics may be necessary if pulmonary infection occurs. The conjunctival sacs should be carefully washed out if eye irritation is severe.

In severe poisoning, amyl nitrite inhalation and sodium nitrite by intravenous injection have been suggested.

A brief review of the management of sulphide poisoning.— R. P. Smith and R. E. Gosselin, *A. Rev. Pharmac. & Toxic.*, 1976, *16*, 189.

The successful treatment of a 47-year-old man with severe hydrogen sulphide poisoning using oxygen, amyl nitrite inhalations for 30 seconds out of each minute for 5 minutes, and then sodium nitrite 300 mg intravenously for 3 minutes. Treatment was aimed at producing methaemoglobinaemia to inactivate the sulphide. In addition he received sodium thiosulphate 12.5 g by intravenous injection.— R. J. Stine *et al.*, *Ann. intern. Med.*, 1976, *85*, 756.

Further references: R. P. Smith and R. E. Gosselin, *J. occup. Med.*, 1979, *21*, 93.

Uses. Hydrogen sulphide is widely employed in many industrial processes.

12833-a

Hydroxyestrone Diacetate. 16α-Hydroxyoestrone Diacetate. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.

$C_{22}H_{26}O_5 = 370.4$.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (diacetate).

Hydroxyestrone diacetate is a derivative of oestrone. It is claimed to have minimal systemic oestrogenic effects when given by mouth but to retain effects on the vaginal mucosa. It is used in the treatment of vaginitis and associated disorders.

Proprietary Names
Colpoginon *(Boizot, Spain)*; Colpogynon *(Laboratories de l'Hepatrol, Switz.)*; Colpormon *(Millet, Arg.; Anphar-Rolland, Fr.)*.

12834-t

Hydroxyethylpromethazine Chloride.

(2-Hydroxyethyl)dimethyl[1-methyl-2-(phenothiazin-10-yl)ethyl]ammonium chloride.

$C_{19}H_{25}ClN_2OS = 364.9$.

CAS — 7647-63-4 (hydroxyethylpromethazine); 2090-54-2 (chloride).

Hydroxyethylpromethazine chloride is an antihistamine.

Proprietary Names
Aprobit *(Recip, Swed.)*.

12835-x

Hydroxymethylnicotinamide. Nicotinylmethylamide; *N*-Hydroxymethylnicotinamide. *N*-Hydroxymethylpyridine-3-carboxamide.

$C_7H_8N_2O_2 = 152.2$.

CAS — 3569-99-1.

Crystals. M.p. 141° to 142°. Sparingly **soluble** in water and alcohol; freely soluble in hot water and alcohol.

Hydroxymethylnicotinamide is a choleretic and has been used in the treatment of various disorders of the gall-bladder.

Proprietary Names
Bilamid *(Cilag, Ger.; Bracco, Ital.; Cilag-Chemie, Switz.)*; Bilamide *(Cilag-Chemie, Belg.)*; Biloide *(Labatec-Pharma, Switz.)*.

12836-r

5-Hydroxytryptophan. 5-HTP; Ro-0783/B. 2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

$C_{11}H_{12}N_2O_3 = 220.2$.

CAS — 56-69-9.

NOTE. The form of 5-hydroxytryptophan used clinically is generally the L-form.

5-Hydroxytryptophan is a precursor of serotonin (see p.1753) and has been used clinically in attempts to treat disorders believed to be associated with serotonin deficiency.

Changes in mood, mostly elevation, were observed in 7 neurological patients without affective disorders and 1 healthy subject given L-5-hydroxytryptophan 100 to 300 mg by intravenous infusion in sodium chloride injection. Carbidopa was also given to reduce the severity of vomiting which always occurred 30 to 90 minutes after infusion and to increase the amount of L-5-hydroxytryptophan entering the brain. Neurotoxicity occurred with doses of 200 mg and above and included dilatation of the pupil, hyperreflexia, ataxia, and dysarthria. There was some similarity to the effects of a cohol.— M. Trimble *et al.* (letter), *Lancet*, 1975, *1*, 583. See also M. H. Greenwood *et al.*, *Br. J. clin. Pharmac.*, 1975, *2*, 165.

Severe insomnia in a 33-year-old woman following a road accident responded to 4 consecutive nightly doses of L-5-hydroxytryptophan totalling 3 g.— M. Webb and J. G. Kirker (letter), *Lancet*, 1981, *1*, 1365.

Manganese poisoning. A beneficial response to DL-5-hydroxytryptophan, up to 3 g daily, was achieved in a patient in whom the symptoms of manganese poisoning failed to respond to levodopa.— I. Mena *et al.*, *New Engl. J. Med.*, 1970, *282*, 5.

Mental disorders. Of 107 patients with endogenous depression given L-5-hydroxytryptophan daily in divided doses by mouth for at least 5 weeks, the majority rapidly obtained a beneficial response.— I. Sano, *Münch. med. Wschr.*, 1972, *114*, 1713, per *J. Am. med. Ass.*, 1972, *222*, 1085. Further studies in depression: N. S. Kline *et al.*, *Am. J. Psychiat.*, 1964, *121*, 379, per *Int. pharm. Abstr.*, 1965, *2*, 918; T. Persson and B.-E. Roos (letter), *Lancet*, 1967, *2*, 987; G. d'Elia *et al.*, *Acta psychiat. scand.*, 1978, *57*, 239; L. J. van Hiele, *Neuropsychobiology*, 1980, *6*, 230.

After oral administration of L-5-hydroxytryptophan with a peripheral decarboxylase inhibitor, mild to moderate improvement was obtained in 6 of 7 chronic undifferentiated schizophrenic patients who were resistant to phenothiazines. Of 4 chronic paranoid schizophrenic patients who were resistant to phenothiazines 2 became worse after treatment with 5-hydroxytryptophan and 1 improved. Some schizophrenic patients might have an abnormality in serotonin metabolism.— R. J. Wyatt *et al.*, *Science*, 1972, *177*, 1124.

Further studies in schizophrenia: V. Zarcone *et al.*, *Archs gen. Psychiat.*, 1973, *28*, 843; R. J. Wyatt *et al.*, *ibid.*, *29*, 597.

Myoclonus. Comment on the use of the investigational drug L-5-hydroxytryptophan in the treatment of myoclonus and the view that in general its use should be discouraged. L-5-Hydroxytryptophan is usually effective in posthypoxic intention myoclonus, a rare condition, but may exacerbate some other myoclonic syndromes. Significant adverse effects, especially gastro-intestinal disturbances, are almost universal, even when given with a peripheral decarboxylase inhibitor such as carbidopa.— R. R. Young, *J. Am. med. Ass.*, 1980, *243*, 1569.

L-5-Hydroxytryptophan with carbidopa was administered to 23 patients with myoclonus and 16 patients with other neurological disorders. Following administration by mouth of maximum doses of 0.4 to 2 g daily with carbidopa 100 to 300 mg daily more than 50% improvement was obtained in 11 of 18 patients with intention myoclonus due to anoxia or other brain damage; only 1 patient obtained no improvement and in 3 it was 90% or more, some patients derived sustained benefit for more than 3 years. No benefit was obtained by 2 patients with athetotic cerebral palsy, 2 with multiple sclerosis, 2 with essential tremor, 4 with cerebellar intention tremor, 1 with infantile spasms, 2 with dystonia musculorum deformans, 2 with central pain syndromes, or 3 with idiopathic epilepsy; some benefit was obtained in 1 patient with myoclonus epilepsy and in 1 of 2 patients with familial essential myoclonus. Side-effects included anorexia, nausea, diarrhoea, and occasional vomiting and were reduced by prochlorperazine or trimethobenzamide and diphenoxylate; prior administration of carbidopa for 1 or 2 days before therapy also reduced the gastro-intestinal side-effects. During the first week of therapy 3 patients developed dyspnoea followed by hyperventilation and lightheadedness, with fainting in 1; pulmonary function tests remained normal. Varying degrees of mental stimulation occurred in 10 patients; these were reversible on dosage reduction and frequently disappeared or diminished after 4 to 6 weeks without reduction, but 2 patients required concurrent administration of perphenazine to maintain their antimyoclonic dosage. Other side-effects included mydriasis, blurring of vision, abdominal pain, and bradycardia.— M. H. Van Woert *et al.*, *New Engl. J. Med.*, 1977, *296*, 70. Comment.— T. L. Munsat, *ibid.*, 101.

Studies suggesting that the treatment of intention myoclonus with L-5-hydroxytryptophan and carbidopa in a 70-year-old man unmasked an abnormality in his ability to metabolise kynurenine and resulted in the development of a scleroderma-like illness.— E. M. Sternberg *et al.*, *New Engl. J. Med.*, 1980, *303*, 782.

Further references: D. Chadwick *et al.*, *Lancet*, 1975, *2*, 434; J. DeLéan and J. C. Richardson (letter), *ibid.*, 870; J. H. Growdon *et al.*, *Neurology, Minneap.*, 1976, *26*, 1135; W. M. Carroll and P. J. Walsh, *Br. med J.*

rastis canadensis L.. ind canadine. Syn- vdrastines: Hope *et et al., ibid.* **1934**, rm. *Bull.* **27**, 1947 *iron Letters* **22**, 619 Haworth, Pinder, *J.* .., *Nature* **165**, 529 n. **293**, 121 (1960). *Letters* **1963**, 859. n. **29**, 2328 (1964); 969). Biosynthesis: 963).

. [α]$_D^{20}$ −50° (c = 218, 238, 298, 316 : 7.8. Freely sol in ne salts hydrolyze

R. Paech, M. V. **vol. IV** (Springer- 116°. [α]$_D^{17}$ -127° cohol; slightly sol 5° soln): 4.2.

as ...erine hemo-

vdro-6-methyl-1,3- -6,7-methylenedi- line. $C_{11}H_{13}NO_3$; 6.76%, O 23.16%. Will, *Ber.* **20**, 88 it. **241,136** (1910). vman, Remfry, *J.* . *J. Appl. Chem.* iopiperonylamine: 913): Rosenmund. im safrole: Kind- Structure study:

ly sol in alcohol. l in cold, moder- alcohol are yel- organic solvents Dobbie, Tinkl-

diotonic; uterine

ige root; yellow ned rhizome and aceae, contg not it. North Amer- erine; canadine.

it $_4N_2$; mol H epn from m. Soc. **76**, 3914 *Inorganic Chem-*

istry vol. **1**, G. Brauer, Ed. (Academic Press, New York, 1963) pp 469-472. Toxicity data: Witkin, *Arch. Ind. Health* **13**, 34 (1956). Toxicology study: Back, Thomas, *Ann. Rev. Pharmacol.* **10**, 395 (1970). Review of carcinogenicity studies: *IARC Monographs* **4**, 127-136 (1974); of toxicology: R. von Burg, T. Stout, *J. Appl. Toxicol.* **11**, 447-450 (1991). Books: L. F. Audrieth, B. A. Ogg, *The Chemistry of Hydrazine* (Wiley, New York, 1951); C. C. Clark, *Hydrazine* (Mathieson Chem., Baltimore, 1953). *Reviews:* Troyan, *Ind. Eng. Chem.* **45**, 2608-2612 (1953); Zimmer, *Chem. Ztg.* **79**, 599-605 (1955); Hudson *et al.*, "Hydrazine" in *Mellor's* vol. VIII, suppl. II, *Nitrogen* (Part 2), 69-114 (1967); Jones in *Comprehensive Inorganic Chemistry* vol. 2, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) p 250-265; H. W. Schiessl in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. **13** (John Wiley & Sons, New York, 4th ed., 1995) pp 560-606.

Colorless oily liq. fuming in air. Penetrating odor resembling that of ammonia. Burns with violet flame. Explodes during distn if traces of air are present, also affected by uv and metal ion catalysts. Can be stored for years if sealed in glass and kept in a cool, dark place. Flash and fire pt 126°F (52°C). Contracts on freezing. d_4^{-5} 1.146; d_4^{0} 1.0253; d_4^{2} 1.024; d_4^{15} 1.011; d_4^{25} 1.0036; d_4^{35} 0.9955. One gallon of commercial product weighs 8.38 lbs. mp 2.0°. bp_{760} 113.5°; bp_{71} 56°; $bp_{5\,atm}$ 170°; $bp_{10\,atm}$ 200°; $bp_{20\,atm}$ 236°. $n_D^{22.3}$ 1.46979; n_D^{15} 1.46444. Dipole moment 1.83-1.90. Dielectric constant (25°): 51.7. Latent heat of fusion (mp): 3.025 kcal/mole; latent heat of vaporization (bp): 9760 kcal/mole (calc). Crit temp 380°, crit pressure 14 atm. Diacidic base. pK_1 (25°): ~6.05. Forms salts with inorganic acids. Highly polar solvent. Powerful reducing agent. Dissolves many inorganic substances. Misc with water, methyl, ethyl, propyl, isobutyl alcohols. Forms an azeotropic mixture with water, bp_{760} 120.3°, which contains 55 mole-% (68.5 weight-%) N_2H_4. LD_{50} in mice (mg/kg): 57 i.v.; 59 orally (Witkin).

Dihydrochloride. $H_4N_2.2HCl$, white crystalline powder, mp 198°. d 1.42. Freely sol in water, slightly in alcohol.

Caution: Potential symptoms of overexposure to hydrazine are irritation of eyes, nose and throat; temporary blindness; dizziness, nausea; dermatitis; burns skin and eyes. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS NIOSH 90-117, 1990) p 124. *See also* Patty's *Industrial Hygiene and Toxicology*, vol. 2E, G. D. Clayton, F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 4th ed., 1994) pp 3435-3441. Hydrazine may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

USE: Chemical intermediate in manuf of agricultural chemicals, spandex fibers and antioxidants. Reducing agent; organic hydrazine derivs; rocket fuel. Dihydrochloride as chlorine scavenger for HCl gas streams.

4810. Hydrazine Hydrate. H_6N_2O; mol wt 50.06. H 12.08%, N 55.96%, O 31.96%. $H_2NNH_2.H_2O$. Prepd from hydrazine sulfate by the action of NaOH, followed by distn under nitrogen.

Fuming refractive liquid, faint characteristic odor. *Violent poison! Causes delayed eye irritation.* d^{21} 1.03. mp −51.7° or below −65° (two eutectics). bp_{740} 118-119°; bp_{26} 47°. n_D^{20} 1.42842. Strong base, very corrosive, attacks glass, rubber, cork, but not stainless V_2A steel or Allegheny stainless 304 and 347. Molybdenum steels such as Allegheny stainless 316 should not be used. Very powerful reducing agent. Miscible with water and alcohol. Insol in chloroform and ether.

Mixture with methanol, *C-Stuff.*

USE: Reducing agent, solvent for inorganic materials. Manuf "Helman" catalyst, consisting of 80% hydrazine hydrate, 19.5% ethanol, 0.5 to 0.05% copper, used to dec hydrogen peroxide in V-2 type rockets. Mixture with methanol as propellant for rocket engines.

4811. Hydrazine Sulfate. Hydrazinium sulfate; hydrazonium sulfate. $H_6N_2O_4S$; mol wt 130.12. H 4.65%, N 21.53%, O 49.18%, S 24.64%. $H_2NNH_2.H_2SO_4$. Prepd by Raschig synthesis: $2NH_3.aq$ - $[Ca(OCl)_2/Na_2CO_3$ colloid] and treatment with H_2SO_4. Starch, glue, or gelatin are used as colloids, and sodium hypochlorite may be used instead of bleaching powder: Adams, Brown, *Org. Syn.* **2**, 37 (1922).

Audrieth, Nickles, *Inorg. Syn.* **1**, 90 (1939). Industrial prepn by the action of sodium hypochlorite on urea in the presence of NaOH: *B.I.O.S. Final Report* **369**; Moncrieff, *Manuf. Chem.* **18**, 177 (1947). Revised lab procedures: Pfeiffer, Simons, *Ber.* **80**, 127 (1947); Adams, Brown, *Org. Syn.* **coll. vol. I**, 2nd ed. (1941), p 309. Crystal structure: Nitta *et al.*, *Acta Cryst.* **4**, 289 (1951); Jönsson, Hamilton, *ibid.* **26B**, 536 (1970). Review of activity and clinical studies in cancer cachexia: J. Gold, *Nutr. Cancer* **9**, 59-66 (1987).

Orthorhombic crystals. Glass-like plates or prisms. d 1.378: Curtis, Jay, *J. Prakt. Chem.* **39**, 39 (1889); d^7 2.016. mp 254°. Sol in about 33 parts water; freely sol in hot water. Insol in alcohol. pH of 0.2 molar aq soln 1.3.

Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

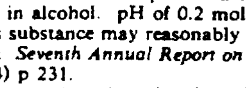
USE: In the gravimetric estimation of nickel, cobalt and cadmium; in the refining of rare metals; as antioxidant in soldering flux for light metals; as reducing agent in the analysis of minerals and slags; in separating polonium from tellurium; in tests for blood; for destroying fungi and molds; in the prepn of hydrazine hydrate.

4812. Hydrazine Tartrate. Hydrazine acid tartrate; hydrazine hydrogen tartrate; hydrazine bitartrate. $C_4H_{10}N_2O_6$; mol wt 182.13. C 26.38%, H 5.53%, N 15.38%, O 52.71%. $H_2NNH_2.C_4H_6O_6$.

Crystals, mp 182-183°. [α]$_D^{20}$ +22.5°. Soly in water at 0° about 6 g/100 ml. pH of a satd aq soln 3.6.

USE: In chemical deposition of metals (silvering mirrors, etc.): Owen, U.S. pat. **2,801,935** (1957 to Merck & Co.).

4813. 4-Hydrazinobenzenesulfonic Acid. *p*-Sulfophenylhydrazine; phenylhydrazine-*p*-sulfonic acid. $C_6H_8N_2O_3S$; mol wt 188.21. C 38.29%, H 4.28%, N 14.88%, O 25.50%, S 17.04%. Prepn by sulfonation of phenylhydrazine: L. Claisen, P. Roosen, *Ann.* **278**, 296 (1894); by the reduction of *p*-diazobenzenesulfonic acid: Th. Zincke, A. Kuchenbecker, *Ann.* **330**, 1 (1903); L. V. Lazeeva *et al.*, **USSR** pat. **1,057,493** (1983 to Tambov Pigment), *C.A.* **100**, 138755q (1984). Used in resoln of 2-pyrazoline cmpds: M. Mukai *et al.*, *Can. J. Chem.* **57**, 360 (1979); in isoln of volatile ketones: W. Treibs, H. Röhnert, *Ber.* **84**, 433 (1951); in analysis of trace amounts of selenium: T. Kawashima *et al.*, *Anal. Chim. Acta* **49**, 443 (1970); *eidem, ibid.* **89**, 65 (1977).



Needles from water, mp 286°. Slightly sol in water, alcohol.

4814. 2-Hydrazinoethanol. 2-Hydroxyethylhydrazine; β-hydroxyethylhydrazine; Omaflora. $C_2H_8N_2O$; mol wt 76.10. C 31.57%, H 10.60%, N 36.81%, O 21.02%. $HOCH_2CH_2NHNH_2$. Prepn from hydrazine monohydrate and 2-chloroethanol: Gansser, Rumf, *Helv. Chim. Acta* **36**, 1423 (1953); from hydrazine monohydrate and ethylene oxide: Gever, O'Keefe, U.S. pat. **2,660,607** (1953 to Eaton Labs.); from hydrazine and ethylene oxide: **Brit. pat. 776,113** (1957 to Olin Mathieson).

Colorless, slightly viscous liquid. d 1.11. One gallon weighs 9.26 lbs. mp −70°. $bp_{17.5}$ 110-130°; bp_{25} 145-153°. Flash pt 224°F (106°C). Misc with water. Sol in the lower alcohols. Slightly sol in ether.

USE: Plant growth regulant.

4815. Hydrazoic Acid. Hydrogen azide; hydronitric acid; triazoic acid; stickstoffwasserstoffsäure (German). HN_3; mol wt 43.03. H 2.34%, N 97.66%. Produced by the action of sulfuric acid on sodium azide: L. F. Audrieth, C. F. Gibbs, *Inorg. Syn.* 1, 77 (1939); using stearic acid: Günther, Meyer, *Z. Elektrochem.* **41**, 541 (1935). Prepn of water and ether solns of hydrazoic acid: W. S. Frost *et al.*, *J. Am. Chem. Soc.* **55**, 3516 (1933); L. F. Audrieth, C. F. Gibbs, *loc. cit.*; P. W. Schenk in *Handbook of Preparative Inorganic Chemistry* vol. **1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 472-474. GC determn: J. M. Zehner, R. A. Simonaitis, *J. Chrom. Sci.* **14**, 493 (1976). Toxic-

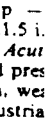
ity study: Grah Review of toxic Patty's *Industr* Clayton, F. E. York, 1981) pp *Comprehensive T istry* **vol. VIII**, Jones in *Compr* Bailar Jr. *et al.*, 276-293.

Mobile liquid. *plosive!* mp − (mg/kg): 21.5 i.

Caution: Acut fall in blood pres hypotension, wea

USE: Industria detonators.

4816. Hydr *ene]-1,1',3,3'-(2H 1,1',3,3'-tetrone;* 322.27. C 67.09 tion of potassiun *J. Org. Chem.* 23 tion of ninhydrin *Chem.* **211**, 907 (



Dihydrate, pris reddish-brown at hot water; sol in aq Na_2CO_3 solns blue color). Can the addn of acid blue color with ar

USE: Reagent fo acids and similar

4817. Hydric water. Marketed 47%, d 1.5; 10%, iodide gas in wate sulfide according Frykholm, *Inorg.* Iodide.

Colorless when or brown on expo can be prevented phorous acid (H_3 for some time are be regenerated wi Jr., *Inorg. Syn.* 2, *air, preferably not* Dissolves iodine. bp_{760} 127°, d 1.70 acid, attacks natu

Caution: Strong

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THERAP CAT: Ex

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HYDRAZINE SULFATE

"...Since hydrazine sulfate provided relief of a wide spectrum of cancer symptoms, it may be recommended for patients with end-stage cancer."

"...virtually no significant untoward side effects..."

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GENERAL INFORMATION

Hydrazine sulfate is an anti-cachexia drug which acts to reverse the metabolic processes of debilitation and weight loss in cancer and secondarily acts to stabilize or regress tumors. Hydrazine sulfate is a monoamine oxidase (MAO) inhibitor and is incompatible with tranquilizers, barbiturates, alcohol and other central nervous system depressants. Foods high in tyramine, such as aged cheeses and fermented products, are also incompatible with MAO inhibitors. The use of tranquilizers, barbiturates and/or alcoholic beverages with hydrazine sulfate destroys the efficacy of this drug and increases patient morbidity.

The U.S. National Cancer Institute (NCI)-published studies of hydrazine sulfate (Journal of Clinical Oncology, June 1994), reported as negative, denied the use of tranquilizers, with the exception of the short-term use of prochlorperazine (Compazine). However, under pressure of an investigation of the NCI studies by the U.S. General Accounting Office ordered by Congress, the NCI in a subsequently published paper (Journal of Clinical Oncology, June 1995) admitted to the widespread use of both benzodiazepine and phenothiazine tranquilizers, which are incompatible with MAO inhibitors, in 94% of all study patients. Moreover, approximately half of these patients were given these tranquilizers on a long-term basis, and some on a continual basis. It was further admitted by the NCI that concomitant drug use (such as tranquilizers, alcohol, barbiturates, etc.) was not computerized and patient

records of such drug use were "incomplete."

There is an abundance of published, positive, peer-reviewed studies on hydrazine sulfate in the medical literature. (Abstracts of some of these published studies are given on the following pages.) These data emanate from major cancer centers both from the United States (randomized, double-blind, placebo-controlled studies and single-arm studies) and Russia (large-scale, multicentric Phase II-equivalent studies). These data indicate the therapeutic action of hydrazine sulfate to extend to all types of tumors.

Hydrazine sulfate has been demonstrated to produce only few and transient side effects. There have been no instances of bone-marrow, heart, lung, kidney or immune system toxicity, or death, reported. Hydrazine sulfate has never been demonstrated to be carcinogenic in humans.

For further information please have your HEALTH CARE PROFESSIONAL (no patients or individuals, please) call the institute.

COLLECTION OF ARTICLES | HOW TO CONTACT SCRI

A collection of articles on Hydrazine Sulfate has been available on this site since 23 October 1996.

General Information
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ARTICLES

The following is a collection of articles based on published studies on Hydrazine Sulfate. You may view the abstract by clicking on the icon to the left. If the title of an article has no hyperlink, then that article is not present on this system (you may still view the abstract).


"Hydrazine Sulfate Influence on Nutritional Status and Survival in Non-Small-Cell Lung Cancer" [Journal of Clinical Oncology 8:9-15, 1990]


"Results of Clinical Evaluation of Hydrazine Sulfate" [VOPROSY ONKOLOGII 36:721-726, 1990]


"Altered Metabolism and Mortality in Patients With Colon Cancer Receiving Chemotherapy" [American Journal of the Medical Sciences 310:48-55, 1995]


"Influence of Hydrazine Sulfate on Abnormal Carbohydrate Metabolism in Cancer Patients with Weight Loss" [Cancer Research 44:857-861, 1984]


"Treatment of Primary Brain Tumors With Sehydrin [Hydrazine Sulfate]" [VOPROSY ONKOLOGII 40:332-336, 1994]


"Hydrazine Sulfate in Cancer Patients With Weight Loss: A Placebo-Controlled Clinical Experience" [Cancer 59:406-410, 1987]


"Anabolic Profiles in Late-Stage Cancer Patients Responsive to Hydrazine Sulfate" [Nutrition and Cancer 3:13-19, 1981]

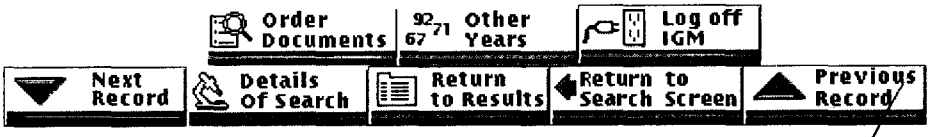

"Effect of Hydrazine Sulfate on Whole-body Protein Breakdown Measured by 14C-Lysine Metabolism in Lung Cancer Patients" [Lancet 2:241-244, 1987]


"Hydrazine Sulfate: A Current Perspective" [Nutrition and Cancer 9:59-66, 1987]


"Experience of the treatment with Sehydrin (Hydrazine Sulfate, HS) in the advanced cancer patients" [Investigative New Drugs 13:89-97, 1995]


"Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients" [Oncology 32: 1-10, 1975]

National Library of Medicine: IGM Full Record Screen



TITLE: Use of hydrazine sulfate in terminal and preterminal cancer patients: results of investigational new drug (IND) study in 84 evaluable patients.

AUTHOR: Gold J

SOURCE: Oncology 1975;32(1):1-10

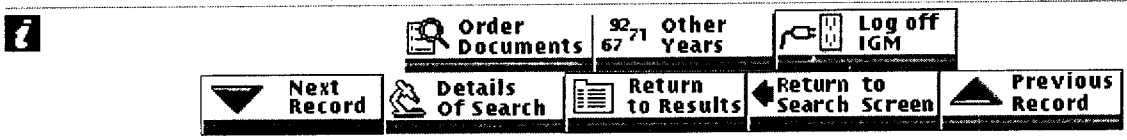
NLM CIT. ID: 76101548

ABSTRACT: In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70% of the cases improved subjectively and 14/84 or 17% improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42%) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50%) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only after the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

MAIN MESH SUBJECTS: Hydrazines/ADVERSE EFFECTS/PHARMACOLOGY/*THERAPEUTIC USE
Neoplasms/*DRUG THERAPY/METABOLISM

ADDITIONAL MESH SUBJECTS: Drug Evaluation
Gluconeogenesis/DRUG EFFECTS
Human

Paresthesia/CHEMICALLY INDUCED
Remission, Spontaneous
PUBLICATION TYPES: **JOURNAL ARTICLE**
LANGUAGE: **Eng**



National Library of Medicine: IGM Full Record Screen

TITLE: Hydrazine sulfate in cancer patients with weight loss. A placebo-controlled clinical experience.

AUTHOR: Chlebowski RT; Bulcavage L; Grosvenor M; Tsunokai R; Block JB; Heber D; Scrooc M; Chlebowski JS; Chi J; Oktay E; et al

SOURCE: Cancer 1987 Feb 1;59(3):406-10

NLM CIT. ID: 87077829

ABSTRACT: Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight (P less than 0.05). In addition, appetite improvement was more frequent in the hydrazine group (63% versus 25%, P less than 0.05). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% versus 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 +/- 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

MAIN MESH SUBJECTS: Cachexia/*DRUG THERAPY/ETIOLOGY
Hydrazines/*THERAPEUTIC USE
Neoplasms/*COMPLICATIONS/DRUG THERAPY

Chapter 5

HYDRAZINE SULFATE

Hydrazine sulfate, a simple, off-the-shelf chemical, dramatically reverses cachexia (ka-KEK-si-a), the wasting-away process that kills two-thirds of all cancer patients. This inexpensive drug, with little or no side effects, also has a clinically documented antitumor action. It causes malignant tumors to stop growing, to reduce in size, and, in some cases, to disappear. A growing number of cancer patients diagnosed as terminal have experienced tumor stabilization and remission through hydrazine sulfate therapy.

About half of all patients who take hydrazine sulfate experience weight gain, restored appetite, extended survival time, and a significant reduction in pain and suffering. Many patients report an increase in vigor and strength and the disappearance of symptoms of the disease, along with feelings of well-being and optimism.

While hydrazine sulfate may not be a sure-fire cancer cure, large-scale clinical trials suggest that it affects every type of tumor at every stage. It can be administered either alone or in combination with cytotoxic chemotherapy or radiation to make the cancer more vulnerable to these standard forms of treatment.

Hydrazine sulfate is now undergoing Phase III trials sponsored by the National Cancer Institute. It is available to patients as a "compassionate IND [Investigational New Drug]," a designation conferred by the Food and Drug Administration on a case-by-case basis, so it is no longer, strictly speaking, an "unconventional therapy." Yet even though hundreds of patients across the country are using the drug, it is not widely discussed or disseminated among practicing physicians and its promise remains largely untapped twenty-four years after it was first proposed as an anticancer treatment by Dr. Joseph Gold. Meanwhile, hydrazine sulfate is widely available in the Com-

monwealth of Independent States (formerly the Soviet Union), where researchers have followed up on Gold's pioneering work with over ten years of investigation supporting the drug's effectiveness.

"We've gone from a red light to a yellow light, and hopefully will go to a green light," says Dr. Gold, director of the Syracuse Cancer Research Institute in Syracuse, New York, which he founded in 1966. Since his discovery in 1968 that hydrazine sulfate can prevent the wasting-away process in cancer patients and inhibit tumor growth, Gold has waged a courageous uphill battle to win acceptance for his nontoxic chemotherapy by the medical establishment.

The American Cancer Society put hydrazine sulfate on its Unproven Methods blacklist in 1976. It condemned and stigmatized the drug following a clinical trial on twenty-nine patients at Memorial Sloan-Kettering Cancer Center in New York. But it is now widely acknowledged that the Sloan-Kettering tests were botched.

When Dr. Gold made an unannounced visit to the hospital in 1974, he discovered, to his horror, that "many patients in the study were either being underdosed or overdosed. Some people who were beginning to show anticachexia response were suddenly being given 90 to 100 milligrams at one time. All this was in clear violation of the drug protocols and of our joint agreements," said Gold.[1] The study's protocol called for patients to receive 60 milligrams once a day for the first three days, twice a day for the next three days, and three times a day for the following six weeks. Therefore, some patients were getting a 67 percent overdose.

In a letter of protest to Sloan-Kettering,[2] Gold pointed out that some patients were receiving a massive, single dose of approximately 120 to 190 milligrams a day (instead of the usual two or three 60-milligram doses), "which quickly wiped out whatever good response they were beginning to show." The study was so poorly executed that it could never be published today, he maintains.

Nevertheless, the damage was done. The ACS's blacklisting of hydrazine sulfate caused Gold's funding to dry up and scared away other researchers from following up on his early papers.

But Gold refused to give up. In 1975, he did a study of the drug's effects on eighty-four advanced cancer patients. A total of 70 percent of them experienced weight gain (or the cessation of weight loss) and reduced pain. Only 17 percent showed tumor improvements. Meanwhile, Russian scientists at Leningrad's Petrov Research Institute were getting impressive results. In one study of forty-eight terminal cancer p[illegible]ts treated with hydrazine sulfate, 35 percent had tumor

stabilization or regression and 59 percent showed "subjective response" (ability to function normally, complete disappearance of marked reduction of pain, and so forth).

As a result of these and other favorable studies, the American Cancer Society announced in 1979 that it was removing hydrazine sulfate from its official blacklist. Only four other "unproven methods" that were once stigmatized on the ACS list as "quackery" have been removed from it. However, the ACS included hydrazine sulfate in the 1979 edition of the Unproven Methods list, and that edition continued to be circulated until 1982. Hydrazine sulfate was finally removed from the list the next time the list was revised, in July 1982.

Tim Hansen, now in his early twenties, of Minneapolis, Kansas, is one person grateful for the existence of hydrazine sulfate therapy. In August 1984, when he was eleven years old, Tim was diagnosed with three inoperable malignant tumors that were growing quickly in his brain. He was placed on radiation therapy, but his health steadily deteriorated until, by early 1985, his weight had dropped to fifty-five pounds. "The radiation harmed his mental functioning, and in January 1985 the surgeon told me that Tim had one week to live," says Gloria Hansen, Tim's mother.

In February, after reading a short item about hydrazine sulfate in *McCall's*, Gloria and her husband, Ray, got in touch with Dr. Gold and Tim was put on hydrazine sulfate therapy by his physicians in Kansas. By August, his weight was up to seventy-five pounds. By early 1987, two of Tim's tumors had completely vanished. In January 1990 a computerized axial tomograph (CAT scan) revealed further shrinkage of the remaining tumor, located in the base of the brain. Dr. Gold plans to keep Tim on the hydrazine sulfate protocol until the tumor is completely gone. Tim graduated from high school in 1990 and is now studying electronics at a trade school, getting A's and B's.

Dr. Gold first stumbled upon hydrazine sulfate's anticancer properties during his methodical quest for a specific type of therapy. Cancer has two principal devastating effects on the body. One is the invasion of the tumor into the vital organs, with the destruction of the organs' functions—the most common cause of cancer death in the public's mind. In reality, however, this accounts for only about 30 percent of the country's half-million annual cancer deaths.

The other devastating effect of cancer is cachexia, the terrible wasting away of the body, with its attendant weight loss and debilitation. In cancer, as in AIDS, patients succumb to the accompanying illness from which they would otherwise survive if not for the [illegible]sting syndrome

"In a sense, nobody ever dies of cancer," notes Dr. Harold Dvorak, chief of pathology at Beth Israel Hospital in Boston. "They die of something else—pneumonia, failure of one or another organs. Cachexia accelerates that process of infection and the building-up of metabolic poisons. It causes death a lot faster than the tumor would, were it not for the cachexia."[4]

Halting the wasting syndrome instead of directly attacking the cancer cells with poison was Dr. Gold's plan of attack. As he explains, "Each of these processes [the tumor invasion of vital organs and cachexia] has its own metabolic machinery, each is amenable to its own therapy, and each is to some degree functionally interdependent on the other. In the interest of treating the totality of malignant disease, each of these processes warrants intervention. Such an approach, dealing with *both* major underpinnings of the cancerous process—mitogenic and metabolic—affords the greatest promise for eliciting long-term, symptom-free survival and the potential for disease eradication."[5]

But what causes cachexia? Cancer cells gobble up sugar ten to fifteen times more than normal cells do. The sugar consumed by the cancer cells is generated mainly from the liver, which converts lactic acid into glucose. (Normal cells are far more efficient users of glucose, which they derive from the food we eat, not from lactic acid.) When cancer cells use sugar (glucose) as fuel, they only partially metabolize it. Lactic acid—the waste product of this incomplete combustion—spills into the blood and is taken up by the liver. The liver then recycles the lactic acid (and other breakdown products) back into glucose, and the sugar is consumed in ever-increasing amounts by voracious cancer cells. The result is a vicious cycle, what Dr. Gold calls a "sick relationship" between the liver and the cancer. The patient's healthy cells starve while the cancer cells grow vigorously. Some healthy cells even *dissolve* to feed the growing tumor.

To break this sick relationship, Gold reasoned, all he needed was to find a safe, nontoxic drug that inhibits *gluconeogenesis* (the liver's recycling of lactic acid back into glucose). In 1968, he outlined his theory in an article published in *Oncology*. "The silence was deafening," he recalls.

A year later, by a remarkable coincidence, Gold heard biochemist Paul Ray deliver a paper explaining that hydrazine sulfate could shut down the enzyme necessary for the production of glucose from lactic acid. Gold had chanced upon an eminently logical way of starving cancer. He immediately tested hydrazine sulfate on mice and found that in accord with his theory, the drug inhibited both gluconeogenesis *and* tumor growth.

Over the years, many dramatic remissions in patients on hydrazine sulfate therapy have been reported. In one case, a sixty-two-year-old woman with widely disseminated cancer of the cervix, in a very debilitated condition, was put on the drug. After one week, a secondary tumor the size of an orange had completely disappeared, much to the amazement of the woman's doctors, and neck nodes had become markedly smaller. After three weeks on the therapy, the patient had gained weight and was active and in good spirits. The woman was discharged from the hospital a short time later.[6]

In 1987, Erna Kamen, a sixty-three-year-old lung cancer patient, was administered hydrazine sulfate after her discharge from a Sarasota, Florida, hospital. "Basically, my mother was sent home to die," says Jeff Kamen, an Emmy-winning television reporter. "She'd lost a significant amount of weight by then, and she had no appetite and virtually no will to do anything."

A doctor had told Jeff's father, Ira Kamen, that hydrazine sulfate offered at least "a shot in the dark." So one Monday in August 1987, a home nurse gave Mrs. Kamen one hydrazine sulfate pill shortly before serving lunch. "On Tuesday morning," recalls Jeff, "there was a commotion in the house. My mother had risen from her bed like the phoenix rising from the ashes. She was demanding that the nurse bring her downstairs so that she could have breakfast with me. . . . When people you love get into this kind of facedown with death you're just incredibly grateful for each moment."[7]

As Jeff describes his mother's recovery, "her searing pain was gone, her appetite returned at a gallop." Within three weeks, her racking cough had vanished and she could walk unaided. "In the months before her death, she went on television with me to tell the nation about hydrazine sulfate. The National Cancer Institute stopped trashing hydrazine sulfate and began referring inquiries to the UCLA Medical School team whose work had validated the effectiveness of the drug long before Erna Kamen began taking it."[8] Jeff attributes his mother's death months later to her being "mistakenly taken off hydrazine sulfate and subjected to an unproven experimental substance."

With cancer patients, hydrazine sulfate is usually administered orally in 60-milligram capsules or tablets, approximately one to two hours before meals. It is given at first once a day for several days, then twice a day, then three or four times daily, depending on the patient's response and the physician's judgment. On such a regimen, many terminal and semiterminal patients have derived considerable benefit, although patients in the early stages of the disease derive the most benefit from the treatment.

Approximately half of the patients to whom the drug is properly administered in the early stages of the disease show an almost immediate weight gain and reversal of symptoms; in some instances, the tumor eventually disappears. The common types of cancer most frequently reported to benefit from hydrazine sulfate therapy are recto-colon cancer, ovarian cancer, prostatic cancer, lung (bronchogenic) cancer, Hodgkin's disease and other lymphomas, thyroid cancer, melanoma, and breast cancer. Some less common types of cancer also benefit.

"Whether hydrazine sulfate should be used in conjunction with other agents seems to be dependent on whether these agents are doing the patient any demonstrable good," according to Dr. Gold. "In the instances in which these agents have been doing good, hydrazine sulfate should be used in conjunction with them. However—and especially with those cases on toxic drugs—in instances in which the drugs have been doing no evident good, it is probably best to withdraw such drugs and use hydrazine sulfate alone." Many alternative therapists disagree. They see hydrazine sulfate as mainly an adjunctive treatment, albeit a potentially powerful one.

Critics have made much of the fact that hydrazine sulfate, a common industrial chemical, is found in such products as rocket fuel, insecticides, and rust-prevention agents. For medical purposes, however, the salt is refined, purified, and used in reagent-equivalent grades. Given to patients in minuscule amounts, it occasionally produces mild, transient side effects such as nausea, dizziness, itching of the skin, drowsiness, and euphoria, but such side effects are minimal, especially when compared with the devastating effects of standard chemotherapy.

A very small percentage of patients undergoing long-term, high-dosage hydrazine sulfate therapy experience pain or temporary numbness in their extremities, but this condition is quickly controlled by reducing the dosage and administering vitamin B_6. In no known cases has hydrazine sulfate depressed or destroyed white blood cells or bone marrow, as conventional chemotherapy often does. In general, toxicity has been exceedingly low or nil.

The most recent study of this drug, however, concluded that hydrazine sulfate appears not to be beneficial and may even have neurological side effects. This study involved a nationwide, twenty-month trial with 291 advanced non-small-cell lung cancer patients, all of whom received chemotherapy. In the double-blind phase, half were given hydrazine sulfate, while the other half received a placebo. Patients receiving hydrazine sulfate had a median survival of 7.62 months, while the

comparable figure for those on placebo was 7.5 months. Hydrazine sulfate had no effect on cancer cachexia, according to Michael Kosty, M.D., an oncologist with Scripps Clinic and Research Foundation in La Jolla, California, who was the study's principal investigator, nor were differences noted between the two groups in anorexia or weight gain. Furthermore, the placebo group rated their quality of life higher than did those patients taking hydrazine sulfate, and some hydrazine sulfate patients experienced loss of sensation and motor function. "Therefore, the best we can say about this drug is that it has no effect and may even be deleterious," Dr. Kosty was quoted as saying in a summer 1992 issue of *ASCO Highlights*, a publication of the American Society of Clinical Oncology.

Dr. Rowan Chlebowski, director of a UCLA research project on hydrazine sulfate, conservatively estimates that the drug could benefit about half a million cancer patients each year in the United States alone.[9] His team has conducted many clinical studies of hydrazine over two decades. Dr. Chlebowski says that the drug's indirect mode of action against tumors is problematic to more cautious investigators. "We found that hydrazine sulfate was an anticachexia agent that indirectly induced antitumor responses without much toxicity. Its action is not directed at cancer cells yet it may profoundly affect them."[10]

Dr. Chlebowski and his colleagues at the Harbor-UCLA Medical Center in Torrance, California, recently found evidence that hydrazine sulfate added to conventional chemotherapy improves the nutritional status and prolongs the life of patients with non-small-cell lung cancer, especially deadly forms of the disease. In the January 1990 issue of the prestigious *Journal of Clinical Oncology*, he reports that earlier-stage patients have a median survival time of at least 328 days, compared to 209 days for the placebo group. There is no curative therapy for this type of lung cancer, so the results, if confirmed, seem promising.

The wasting syndrome seen in cancer patients is also a prime risk factor for AIDS patients with Kaposi's sarcoma. There is evidence that hydrazine sulfate's capacity to stop cachexia may save many AIDS patients. Currently, Dr. Chlebowski is planning a study to test hydrazine sulfate as an anticachexia agent in patients who are infected with HIV and have lost weight.

Even though hydrazine sulfate is now undergoing extensive Phase III trials sponsored by the National Cancer Institute, resistance to this inexpensive, nontoxic chemotherapy in orthodox medical circles persists. Dr. Vincent DeVita, former director of the NCI, told a

Vashington Post reporter in 1988 that he thought hydrazine was a no-hum idea." Dr. Gold, until recently, has been frozen out of the war on cancer." Two articles on cachexia published in July 1990 in he prestigious *Cancer Research* journal fail to reference any of Gold's ath-breaking work, and one even denies there is any effective eatment for the wasting-away syndrome.

Dr. Gold, who does not treat patients, says that the cost of hydrane, at most, should be nominal—comparable to the daily cost of sulin and other supplies for diabetics. "Until a pharmaceutical company sponsors the drug through the FDA, it will not be widely in use," e predicts, adding, "However, with the new studies, drug companies ave suddenly begun to take notice of this most exemplary drug."

Resources

Syracuse Cancer Research Institute
Presidential Plaza
600 East Genesee Street
Syracuse, NY 13202
Phone: 315-472-6616

or further information on hydrazine sulfate and details on treatment.

Reading Material

The Cancer Industry: Unravelling the Politics, by Ralph W. Moss (see Appendix A for description).

Part Two

IMMUNE THERAPIES

The immune system is your body's major line of defense in the battle against cancer and infection. Specialized cells in your immune system can recognize cancer cells as foreign and destroy them. The aim of immune therapies is to bolster those parts of the immune system that combat and eliminate cancer cells. Most other alternative therapies, though not strictly immunotherapies, also stimulate the body's natural defenses.

Several forms of orthodox immunotherapy are currently being explored in clinics and cancer centers. They are still used almost totally as adjuncts to chemotherapy, radiation, and surgery. While these orthodox immune therapies are said to hold great promise, they remain largely experimental. In contrast, the three alternative immune therapies discussed in Part Two of *Options* are used by many patients as full-fledged programs, though these treatments have been condemned, persecuted, or shunned by the medical establishment without an in-depth investigation into their possible merit. Most conventional physicians, trained to be aggressive in their approach to fighting disease, are cool toward the idea of strengthening the body's gentle self-healing powers and its natural resistance to cancer.

Cancer cells are believed to form every day in the healthy person, but a strong immune system can easily detect and destroy them before they have an opportunity to divide and proliferate. Unfortunately, for various reasons—poor nutrition, the massive pollution in our environment, stress, aging—the immune system sometimes fails to recognize the cancer cells as an enemy, and the cancer begins its slow, insidious growth over a number of years while you continue to be unaware of it.

Your immune system is normally on constant alert, scanning your body for "foreigners" such as bacteria, viruses, and abnormal cells. As soon as a foreign body is recognized, your whole system springs into action. Highly mobile *natural killer cells*, specialized to destroy foreign-

ers, are your body's first line of defense. If the cancer cells evade the natural killer cells, they proliferate and manufacture *antigens*, which are telltale substances detected by the *T-cells*, your immune system's second line of defense against tumor growth. Specialized T-cells (or *T-lymphocytes*) destroy cancerous and virus-infected cells. (The "T" in *T-cell* stands for "thymus-derived" because these white blood cells, created in the bone marrow, are carried to the thymus gland, which transforms them into T-cells.) Other white blood cells, *macrophages* (Greek for "big eaters"), ingest the cancer cells. A wide range of other cells and substances that make up the immune system help to orchestrate a coordinated attack against almost any invader.

Altogether, there are five major types of orthodox immunotherapy. The first is *BCG*, a tuberculin vaccine used in the treatment of cancer that stimulates macrophages to kill cancer cells. Consisting of a weakened strain of the tuberculosis bacillus, BCG (which stands for *bacillus Calmette-Guérin*) apparently works best when combined with chemotherapy; yet as a solo treatment, it has brought about some complete remissions and many cases of temporary or prolonged remission. Used by conventional as well as alternative doctors, BCG has been particularly successful in treating malignant melanoma. It appears to work well when injected directly into tumors visible on the skin, though it has also been used to treat lung cancer and other forms of the disease. One of the researchers who discovered BCG's anticancer potential was Dr. Lloyd Old, who later became director of the Sloan-Kettering Institute for Cancer Research.

Interferon is a family of proteins produced by the white blood cells in response to viral infection. It stimulates the production of macrophages and *lymphocytes* (white cells), blocks the growth of tumor cells, and transforms some lymphocytes into natural killer cells. Hyped as a wonder therapy and miracle cure when it was first synthesized in 1980, synthetic interferon turned out to be very expensive and have toxic side effects. It produces fever, chills, and muscle contractions so severe that they may require morphine.[1] Today, interferon is approved for use in the treatment of two rare forms of cancer, hairy-cell leukemia and juvenile laryngeal papillomatosis. It may have limited value in a number of other rare conditions. The FDA approved its use for AIDS patients in 1988, but it has largely been a failure in ARC-AIDS trials. Infected people who received it had flu-like symptoms, fatigue, swelling, headaches, and even hallucinations.

Interleukin-2, a protein produced by the T-cells, was also hyped by the cancer industry and the major news media as a cancer breakthrough. The results to date, however, have been disappointing. IL-2, as it is called, has reportedly been effective in some patients with melanoma and renal cancer, but its drawbacks are major and became evident early on. Charles Moertel, M.D., of the Mayo Clinic, charged that IL-2 is highly toxic, hugely expensive, and not particularly effective.[2] Its side effects include fever, chills, malaise, swelling of the spleen, anemia requiring multiple transfusions, severe bleeding, shock, and confusion. Treatment with IL-2, according to Dr. Moertel, may require weeks of hospitalization in an intensive care unit "to survive the devastating toxic reactions."[3] After a few patients died because of interleukin-2, the National Cancer Institute, which had eagerly presented it to the public as a miracle drug, withdrew such claims.[4]

Tumor necrosis factor (*TNF*), produced in the body in minute quantities, seems to kill cancer cells by destroying their cell membranes, although why this happens is not clear. Side effects occur regularly; most patients develop fever and chills as well as some nausea and vomiting.[5] Injected into cancerous mice, TNF causes their tumors to melt away. It is currently being tested to determine its potential efficacy in treating human cancer patients. Some observers believe that TNF, upon which the cancer establishment has spent millions, is simply *tumor antibody*, one of the four blood fractions used by Lawrence Burton, pioneer of a nontoxic immune therapy used in the diagnosis and treatment of cancer (see Chapter 6).

Monoclonal antibodies are synthetic antibodies created through gene-splicing, fusing a cancer patient's white blood cells with his or her cancer cells. When these bizarre *hybridomas* are reintroduced into the patient's body, they manufacture specific antibodies said to attack only the cancer cells. Attached to anticancer drugs or natural toxins, monoclonals serve as "guided missiles" by directing the antibodies they manufacture toward their malignant prey. Still in the investigative stage, monoclonals—like interferon, interleukin-2, and TNF—promise to be tremendously expensive, a boon to the pharmaceutical-medical monopoly if they are ever used in cancer treatment. They are frequently touted by the media as the next cancer breakthrough.

The American Cancer Society freely admits that it will take "many years to find the proper role of these [orthodox immunotherapy] agents in cancer treatment."[6] Observers say this means twenty years or more. Meanwhile, the ACS continues to use its enormous power and influence to restrict or suppress safe, nontoxic cancer therapies that have produced remarkable clinical results in human beings, such as the immune therapies of Lawrence Burton, Ph.D. (Chapter 6) and Virginia Livingston, M.D. (Chapter 7), or the biologically based therapy of Stanislaw Burzynski, M.D. (Chapter 2).

Ironically, *Coley's mixed bacterial vaccine*, which has perhaps shown

a greater cure rate than any other cancer treatment, is totally unavailable. Dr. William Coley (1862–1936), an eminent New York City surgeon and Sloan-Kettering researcher, in the 1890s developed a vaccine made of bacterial toxins that activated immune-resistance mechanisms in cancer patients and cured hundreds. His daughter, Helen Coley Nauts, D.Sc., has preserved and carried forward his important work. Yet, despite the successful use of bacterial vaccines amply reported in the medical literature since the turn of the century, today's big drug companies have no interest in what they view as merely an unprofitable item.

Staphage Lysate, a nonspecific bacterial vaccine made from *staphylococci,* is legally sold today as a specific therapy for acute and chronic staphylococcal infections. Unofficially, it has been widely used by pragmatic doctors who have had encouraging results in treating multiple sclerosis, cancer, herpes, allergies, arthritis, asthma, and many other conditions.[7] Relatively inexpensive and almost totally nontoxic, Staphage Lysate can be inhaled, injected, or taken orally. It is known to increase the production of T-lymphocytes and to induce the natural formation of interferon and *interleukin-1,* the predecessor of interleukin-2.

Immune therapies, whether orthodox or alternative, are generally used as a treatment of last resort after patients have received toxic chemotherapy or radiation. Many doctors believe that the prior use of immune-destroying, often carcinogenic conventional treatments lowers a patient's chances for recovery through immune therapy. Chemotherapy often accomplishes the destruction of the immune system, and radiation can cause severe, prolonged immune deficiency. At any one time, there are thousands of cancer patients in the United States undergoing aggressive chemotherapy who would benefit from any immune-enhancing measures whatsoever, even supportive nutrition or vitamin supplementation.

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Hydrazine Sulfate in Cancer Patients With Weight Loss

A Placebo-Controlled Clinical Experience

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Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight ($P < 0.05$). In addition, appetite improvement was more frequent in the hydrazine group (63% *versus* 25%, $P < 0.05$). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% *versus* 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 ± 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

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WEIGHT LOSS commonly accompanies cancer development and is associated with an adverse prognosis.[1-3] Although intensive caloric support now can be provided such patients, clinical trials evaluating caloric provision alone have not reported improved outcome for chemotherapy-treated populations with advanced cancer.[4-6] As a result, consideration of potential mechanisms underlying the development of weight loss in the cancer population has led to development of alternative strategies for clinical intervention in these patients. Altered glucose metabolism is a common metabolic abnormality in cancer patients with weight loss,[7-13] and it has been suggested that the inappropriate activation of pathways of glucose metabolism leads to futile cycling and cachexia development in this population.[14] If this hypothesis is correct, amelioration of the abnormal carbohydrate metabolism could provide a therapeutic approach to the adverse outcome associated with cachexia development in the cancer-bearing host.

We previously demonstrated that hydrazine sulfate is metabolically active, improving the abnormal glucose tolerance and reducing the increased glucose production rates seen in cancer patients with weight loss.[13] We now report clinical observations on short-term hydrazine sulfate use in a cancer population with weight loss using a prospective placebo-controlled study design.

Materials and Methods

The criteria for inclusion in this trial were: a diagnosis of advanced cancer; weight loss greater than 10% from usual body weight; absence of severe hepatic or renal dysfunction (bilirubin greater than 3 mg/dl and/or creatinine greater than 2 mg/dl); and normal mental status. Patients with a known history of diabetes mellitus or those receiving corticosteroid therapy were ineligible. Patients with ascites or clinically significant edema were not entered to avoid confounding weight determinations. Patients were entered either prior to receiving systemic chemotherapy or when a new systemic therapy program was initiated

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for disease progression. Measurable disease parameters were not required, and concurrent chemotherapy was permitted. Both initial and repeat assessment of all study parameters, however, were conducted at least 2 days before and 4 weeks after chemotherapy administration.

After informed consent was obtained, patients underwent an initial assessment of nutritional parameters, including caloric intake as described below. Patients subsequently were treated with capsules containing hydrazine sulfate (60 mg) or placebo which were prepared by Anabolic, Inc. (Irvine, California). Hydrazine sulfate was given under IND 17, 671 from the Food and Drug Administration (FDA) (obtained by Dr. Chlebowski). All institutional requirements for human subjects review were met. The treatment program consisted of an escalating schedule of capsules containing either hydrazine sulfate or placebo until the full dosage of 60 mg, 3 times/d given before meals, was reached beginning on the 8th day. This program was based on the extensive Russian experience.[15] Patients were contacted weekly to assess compliance and kept daily compliance diaries. The validity of daily compliance diaries was checked against intake based on returned prescription bottles. Following 30 days of either agent, the assessment of body weight, caloric intake, and ther parameters was repeated.

During the initial and repeat evaluation, all patients received determination of body weight measured on the same printing scale; anthropometrics, including tricep skinfold thickness, mid-arm muscle circumference, and serum albumin; caloric intake using a 24-hour dietary recall history obtained by nutritionists and computer analyzed to give protein, carbohydrate, fat, and energy contents of the diet. Expected caloric intake was normalized for each patient by weight based on a calculated recommended daily allowance (RDA). Toxic effects of treatment and influence on appetite were determined by questionnaire.

In a subset of 14 patients, blood samples for hydrazine sulfate circulatory levels were obtained as a morning sample taken at least 9 hours from the last oral dose following 30 days of treatment. Hydrazine sulfate levels were measured using a defined[16,17] spectrofluorometric assay in which reaction of hydrazine sulfate with dimethylaminobenzaldehyde produces a colored derivative. Fluorescence was subsequently determined in an Aminco Bowman (Silver Spring, MD) spectrophotofluorometer with an excitation wavelength of 466 nm and emission wavelength of 546 nm.

All patients were given defined, uniform dietary counselling based on nutritional status at entry to insure comparability of dietary information available to patients on hydrazine or placebo treatment. The nutritional guidelines all patients were provided with were designed to duplicate a routine clinical dietary assessment that would be expected to be a component of a cancer patient's standard clinical management. Enteral tube feedings or parenteral nutritional support was not given any patient while on study.

TABLE 1. Pretreatment Characteristics of Cancer Patients Receiving Hydrazine Sulfate or Placebo

	Treatment received	
	Hydrazine	Placebo
Number entered	71	30
Age in years		
Median	56	59
Range	32–77	36–77
Sex (% Male)	61%	65%
Disease type		
Lung	46	15
Colon	13	4
Other breast	4	3
Esophagus	2	3
Nasopharyngeal	3	1
Hepatocellular	1	2
Ovarian	2	1
Prostate	0	1
Performance score		
(0 or 1)	14%	23%
(2 or 3)	86%	77%
Nutritional status		
% Weight loss (mean)	17%	14%
Caloric intake		
≥90% of RDA	39%	41%
<90% of RDA	61%	59%
Albumin gm/dl (Mean)	3.4	3.3
Concurrent chemotherapy	78%	74%

RDA: recommended daily allowance.

A total of 101 patients with advanced cancer underwent initial evaluation. Sixty-one consecutive patients (including all 30 patients given placebo and 31 given hydrazine) were randomly assigned treatment in a double-blind fashion with treatment assignment based on published random-number tables. An additional 40 patients received hydrazine sulfate and represented a consecutive series of patients seen in the Clinical Research Center meeting entry criteria for the trial. Statistically significant differences between hydrazine and placebo groups relative to pretreatment clinical factors were sought using chi square contingency table analyses and Student's *t* test. The statistical differences between hydrazine and placebo treatment were determined using the two-group *t* test.

Results

A total of 101 patients with a variety of advanced cancers underwent initial evaluation. Patients receiving hydrazine sulfate or placebo were comparable with respect to tumor type, age, sex, performance score, nutritional parameters and chemotherapy experience (Tables 1 and 2). The compromised nutritional status of the study pop-

TABLE 2. Concurrent Chemotherapy of Cancer Patients Receiving Hydrazine Sulfate or Placebo According to Disease Type

Chemotherapy given	Study arm	
	Hydrazine	Placebo
Lung cancer (n)	46	15
PACcO	15	4
PVB	12	7
ACcO	9	2
ACO	2	0
No chemotherapy	8	2
Colon cancer (n)	13	4
5-FU	2	1
5-FU + vitamin K	7	1
No chemotherapy	4	2
Other disease sites (n)*	12	11
No chemotherapy	4	3

P: cisplatin (Platinol); A: doxorubicin, (Adriamycin); C: cyclophosphamide; c: CCNU; O: vincristine (Oncovin); 5-FU: 5-fluorouracil; V: vinblastine; B: bleomycin; 5-FU + vit K: 5-fluorouracil plus vitamin K_3 (Synkavite).

* The patients with other disease sites received a variety of regimens which included cisplatin in 62% and 50% of instances for the hydrazine and placebo group, respectively.

ulation is demonstrated by the 16% average weight loss experienced by the overall population. Of this advanced disease population with weight loss, 58 patients were able to complete repeat evaluations after 30 days of treatment (41 were given hydrazine; 17, placebo). Early disease progression and/or death accounted for almost all cases not having repeat study. Only two patients refused repeat evaluation.

The influence of 30 days of hydrazine sulfate or placebo therapy on study parameters for all entered patients who underwent repeat evaluation is outlined in Table 3. Weight was maintained or increased in a higher proportion of patients receiving hydrazine sulfate compared to placebo therapy (83% *versus* 53%, respectively; $P < 0.05$). The use of weight loss as a study parameter was not compromised by the development of ascites or significant edema, as this did not occur in any patient over the 30 day period of observation. Anthropometrics were unchanged over the 30-day study period. Caloric intake was only slightly higher in the hydrazine treated population. When all patients experiencing an increase in caloric intake were considered, however, weight gain was seen in a significantly higher proportion of patients receiving hydrazine sulfate while increasing caloric intake compared with those who increased caloric intake while receiving placebo. The results using hydrazine sulfate were closely comparable in the 31 patients entered as part of the randomized trial when compared with the 40 patients added as a consecutive series. The results for the patients receiving hydrazine or placebo who were entered as part of the randomized trial were: weight maintained or increased, 71% *versus* 53%; improvement in appetite, 63% *versus* 25%; caloric intake increased, 69% *versus* 37%; and increased caloric intake associated with weight gain, 77% *versus* 53% for the hydrazine *versus* placebo patients respectively. In addition, results in groups receiving or not receiving concurrent chemotherapy reflected those obtained in the entire group.

TABLE 3. Influence of 30 Days of Hydrazine Sulfate or Placebo on Nutritional Status of Cancer Patients With Weight Loss

	Hydrazine n = 41*	Placebo n = 17
Weight maintained or increased (>2.5 kg)	83%†	53%
Improvement in appetite	63%†	25%
Caloric intake increased (>10% over baseline)	51%	37%
Increased caloric intake associated with weight gain (>2.5 kg)	81%†	53%

* Number completing initial and repeat study.
† $P < 0.05$ hydrazine compared to placebo group.

Thirty-five patients with cancer other than small cell lung cancer (the predominant tumor type studied) completed serial evaluation, with 26 receiving hydrazine sulfate and nine receiving a placebo. In the lung cancer patients, weight maintenance or increase was achieved in 83% of those receiving hydrazine sulfate compared with 33% of those receiving the placebo.

The short term hydrazine sulfate regimen used in this trial was well tolerated by study participants. Compliance forms were returned by 90% of patients who completed repeat evaluations, and indicated that 95% of the scheduled dose was taken by the study population completing 30 days of therapy. The mean maintenance plasma hydrazine sulfate levels obtained from a subset of 14 patients ranged from 0 to 89 ng/ml with a mean value of 45 ± 16 ng/ml. Clinical toxicity of patients receiving hydrazine sulfate was limited largely to mild to moderate nausea and lightheadedness with 71% of patients reporting no toxic effects from hydrazine use (Table 4). Treatment was discontinued for toxic effects in 10% of patients receiving hydrazine; while 6% of patients receiving placebo had treatment stopped for "toxic effects." Significantly, parasthesias or hypoglycemic symptoms were not reported by any patient receiving hydrazine in this trial.

Discussion

Short-term administration of hydrazine sulfate was better than a placebo in maintaining body weight and improving appetite in patients with advanced cancer in the current clinical experience. The weight effect apparently resulted from an increase in the effectiveness of the ingested calories, since a higher proportion of patients

who increased their caloric intake on hydrazine were able to maintain or improve their body weight. The association that we have reported[18] between weight maintenance and improved glucose metabolism in hydrazine-treated cancer patients suggests that interruption of abnormal metabolic pathway function may underlie the improved nutritional status seen with hydrazine sulfate in the current trial. If this hypothesis can be confirmed, hydrazine sulfate could represent one of a new class of metabolic/hormonal agents[19-21] directed at influencing the abnormal metabolism seen frequently in patients with cancer.

No prior clinical experience with hydrazine sulfate in cancer patients has prospectively evaluated caloric intake or included a placebo control population. Single-arm studies involving 348 Russian and 84 American patients with cancer have emphasized subjective parameters.[15,22] In the American experience, Gold[22] reported that 70% of the treatment group demonstrated subjective improvement, including increased appetite with either weight gain or cessation of weight loss, increased strength and improved performance status, or decreased pain, as measured by need for analgesics. In the Russian experience, Gershonovich[15,23] reported that 50% of patients receiving hydrazine sulfate as their sole therapeutic intervention ieved moderate or marked improvement in cachexia with associated favorable symptomatic effects on appetite and pain. Not all clinical studies of hydrazine sulfate have shown benefit. In three small trials of hydrazine sulfate (all entering less than 30 patients) where reduction in tumor size was used as a major therapeutic endpoint, little benefit was reported.[24-26] The clinical effects of hydrazine sulfate on body weight observed in the current study in conjunction with the metabolic effects of hydrazine that we reported in 1984[12] now provides a strong rationale for further studies designed to assess the impact of hydrazine sulfate on clinical outcome in defined cancer populations.

Surprisingly, thirty-seven percent of weight-losing cancer patients given placebo in this trial increased their caloric intake by more than 10%, and 53% of the placebo group maintained or increased their body weight over the 1-month observation period. This result in the placebo population may have been related to the nutritional counseling that was given in identical fashion to patients on both treatment arms in this study. Placebo controls clearly are important in trials designed to alter and assess nutritional parameters in cancer populations.

The study protocol employed in our trial was not designed to assess the influence of hydrazine sulfate on tumor growth characteristics. The short 30-day period of treatment and entry criteria preclude assessment of hydrazine sulfate influence on this parameter. Almost all of our patients with advanced solid tumors refractory to initial therapy, however, demonstrated no change in tumor dimensions during the 1-month period of observation.

TABLE 4. Patient Tolerance of Hydrazine Sulfate or Placebo Treatment

	% of Patients Treated	
	Hydrazine	Placebo
No toxic effects	71%	84%
Nausea and vomiting		
Mild	12%	12%
Moderate	5%	0%
Light-headedness	17%	6%
Treatment discontinued for toxic effects	10%	6%

The relative lack of toxicity of short-term hydrazine sulfate administration in a 60 mg 3 times/d schedule to a large cancer population receiving other concurrent chemotherapy treatment was noteworthy. In the previous limited clinical experience,[15,22,23] only one report has emphasized significant toxicity; Ochoa and coworkers[24] reported a 50% incidence of polyneuritis associated with hydrazine sulfate use in a 29-patient experience. In three trials[15,22,25] and the present report, polyneuritis was seen in less than 1% of the more than 500-patient cumulative experience. The lack of toxicity in the current experience can be documented further by the good compliance reported by the patients in their diaries. The latter result is interesting considering the somewhat wide range of hydrazine sulfate maintenance circulatory levels observed in the pharmacokinetic component of this trial. However, these results are consistent with developing pharmacokinetic information regarding the half-time of oral hydrazine sulfate administration.[17] These data suggest that future clinical trials involving hydrazine sulfate should include determination of chronic circulatory levels to assess hydrazine sulfate bioavailability and permit correlation with metabolic, nutritional and clinical endpoints.

Conclusion

This experience with hydrazine sulfate in an advanced cancer population points to a potential role for this agent in maintaining weight in patients with cancer cachexia. Whether maintenance of body weight under these conditions will be associated with improvement in important clinical outcome variables and overall survival will require future prospective, long-term, placebo-controlled evaluation in cancer populations with less advanced disease given defined systemic therapy. Such studies in the non-small cell lung cancer population are currently in progress.

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Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients

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Key Words. Hydrazine sulfate therapy in advanced cancer patients · Treatment of advanced human cancer with anti-gluconeogenic drugs · Interruption of cancer cachexia as a means of cancer chemotherapy · Interruption of gluconeogenesis as a means of cancer chemotherapy

Abstract. In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70 % of the cases improved subjectively and 14/84 or 17 % improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42 %) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50 %) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

Hydrazine sulfate has been used as an investigational new drug (IND) for over 1 year in the treatment of advanced cancer. Its proposed mechanism of action is as a gluconeogenic blocking agent at the phosphoenolpyruvate carboxykinase (PEP CK) reaction, attenuating host energy loss as a result of increased gluconeogenesis in cancer and therefore interrupting the *systemic* cycle of *tumor-energy gain–host-energy loss* (tumor growth–host cachexia) (1, 2). Early reports indicated that hydrazine sulfate, administered orally to advanced cancer patients, resulted in marked subjective and objective improvements (3), subjective improvements including increase in appetite, cessation of weight loss and/or

weight gain, improved performance status, and decrease in pain; objective improvements included measurable reduction in tumor size and reduction in or disappearance of neoplastic-associated disorders (effusions, jaundice, etc.). Duration of improvements was reported as variable and side effects, minimal. In further reports (4), in which hydrazine sulfate was used in conjunction with conventional chemotherapy in patients with disseminated neoplasia, it was unclear as to which type of therapy resulted in the reported subjective and objective improvements. The present report, undertaken as a pharmaceutical-sponsored IND study and representing a series of 84 evaluable cases of various terminal and preterminal cancer patients, indicates a high degree of anticancer activity in patients treated with hydrazine sulfate alone.

Procedures and Protocols

Physician selection. This study was the result of separate inputs of many clinicians – oncologists as well as others – whose participation was under pharmaceutical IND sponsorship. As such, this study is designated as 'uncontrolled'.

Patient selection. Patients with any type of disseminated neoplasia, who no longer responded to chemotherapy and/or radiation, were considered eligible for hydrazine sulfate therapy. A minimum prognosis of 2 months was recommended.

Drug and protocol. The drug consisted of 100 % purity hydrazine sulfate mixed with an inert starch in capsular form (pharmaceutical IND preparation) for oral administration. Protocol of drug administration was as follows: 60 mg q.d. × 4; 60 mg b.i.d. × 4; then 60 mg t.i.d. as maintenance. In patients weighing less than 50 kg, dosages were halved (i.e., 30 mg q.d. × 4; 30 mg b.i.d. × 4; then 30 mg t.i.d.). In the event that a b.i.d. schedule produced satisfactory results, this dosage schedule was maintained at the clinician's discretion. In no event was a single dosage ever to exceed 60 mg.

Concurrent anticancer medication. The continuing use of concurrent anticancer medication was acceptable if it was no longer producing a demonstrable anticancer effect by itself.

Data presentation. A 4-sheet data page ('Patient Report Form') was required to be completed by the clinician during the course of treatment of each patient. These data sheets included the following information: detailed history, site of tumor and metastases, prior treatments (defined in this study as any type of anticancer therapy given within 3 months of the initiation of hydrazine sulfate therapy; prior treatment data included dates of therapy, types and quantitation), concurrent medications, performance status evaluation, objective tumor size and site evaluations, subjective observation ratings and check list, laboratory data, clinician's statement of patient evaluation prior to hydrazine sulfate therapy, clinician's statement of evaluation of results of hydrazine sulfate therapy, clinician's evaluation of side effects of hydrazine sulfate therapy, and clinician's signature.

Criteria for designation as 'improvement'. Designation of subjective improvements was made on the basis of improvements indicated in the subjective observations rating check list and/or affirmation of improvement in the clinician's statement under 'clinician evaluation' section. In general a subjective improvement was based on a quantitatively measurable or estimable parameter such as strength (number of hours ambulatory, quality of ambulation, etc.), appetite (food intake), weight (scale measurement) and pain (quantitative need for analgesics). Objective improvements were designated on the basis of measurable reduction in

tumor size, long-term (1 year or more) 'stabilized condition' in a previously rapidly growing neoplasm, and disappearance of or reduction in neoplastic-associated disorders. Each case in this category was to be supported by related laboratory measurements, where possible.

Criteria for designation as 'nonevaluable'. Cases were deleted from evaluation for any of the following reasons: (a) inadequate prognosis: patient survival of less than 3 weeks; (b) inadequate drug trial: drug trial of less than 3 weeks; (c) insufficient data submitted on Patient Report Form: no evaluation possible, and (d) concurrent treatment with newly initiated cytotoxic chemotherapy: patient response nonevaluable.

Results

Of a total number of 158 cases submitted in the study, 84 were evaluable and 74 nonevaluable. Of the evaluable cases 14 (17 %) were categorized as 'objective (and subjective) improvement', 45 (54 %) as 'subjective improvement only', and 25 (30 %) as 'no improvement'. The indicated overall improvement

Table I. **Categorization of evaluable cases in Investigational New Drug study of hydrazine sulfate**

Site and/or type of primary tumor	Objective and subjective improvements	Subjective improvement only	No improvement	Total cases
Brain (astro, glio)	2	0	0	2
Breast (all)	2	6	2	10
Colorectal-gastric	2	12	8	22
Gallbladder	1	0	0	1
Hodgkins, stage IV	0	0	2	2
Liver (primary)	0	0	1	1
Lung (all)	2	11	2	15
Melanoma	0	1	2	3
Neurosarcoma (neck)	0	1	0	1
Ovary (all)	1	3	1	5
Pancreas	1	4	3	8
Primary unknown	0	2	0	2
Prostate	0	1	2	3
Squamous cell (neck)	0	1	0	1
Testis	0	1	0	1
Tonsil (palatine)	1	0	0	1
Urinary bladder, ureter	0	1	2	3
Uterus (cervix)	1	1	0	2
Uterus (endometrial)	1	0	0	1
Total	14	45	25	84

Table II. Nonevaluable cases: reasons for exclusion from evaluation

Inadequate prognosis survival time, weeks			Inadequate drug trial, weeks on drug			Insufficient data	New concurrent cytotoxic chemotherapy	Total cases
0–1	1–2	2–3	0–1	1–2	2–3			
11	11	9	8	6	11			
31			25			15	3	74

rate was 59/84 cases, or 70 %. Of the nonevaluable cases, 31 (42 %) were included under 'inadequate prognosis', 25 (34 %) under 'inadequate drug trial', 15 (20 %) under 'insufficient data', and 3 (4 %) under 'newly initiated cytotoxic chemotherapy'. Categorization of evaluable and nonevaluable cases is given in tables I and II, respectively.

'Improvements'

Improvements were noted in tumors from almost all of the 19 reported sites of origin. No particular site of origin or tumor type was 'most susceptible' to hydrazine sulfate therapy, although the largest number of cases came from colorectal and lung carcinoma, which reflects the general incidence of these diseases in the population. The duration of improvement was variable, being reported from very temporary (1 week) to in excess of 1 year and continuing. It was possible to obtain follow-up reports in only less than half of the improved cases.

Objective responses. Of the 14 reported objective responses, 7 (50 %) showed measurable tumor regression; 2 of these were accompanied by a disappearance of or reduction in neoplastic-associated disorders (effusions, jaundice, etc.). An additional 2 (14 %) of the 14 cases were classified as long-term 'stabilized condition', both of which represented preterminal lung cancers whose disease had been rapidly progressive prior to hydrazine sulfate therapy. They are currently both alive and well 17 and 18 months after initiation of hydrazine sulfate therapy, respectively; neither are on any kind of concurrent anticancer therapy. The remainder of the 5 (36 %) cases were classified as objective responses on the basis of amelioration of neoplastic-associated disorders, accompanied by marked subjective improvements. (In this regard all 14 cases showed subjective improvements.) All objective responses were also accompanied by tumor-related laboratory improvements, where measured.

Subjective responses. A total of 45 cases displayed subjective improvements only; this number, added to the foregoing 14 cases, gave a combined total of 59 subjectively improved cases. 48 (81 %) of these showed an increase in appetite

Table III. Response analysis in improved cases

	No concurrent or prior anticancer therapy	Concurrent anticancer (incl. cytotoxic) therapy	Concurrent steroid therapy only	Concurrent steroid and prior cytotoxic therapy	Concurrent steroid and prior radiation therapy	Prior cytotoxic therapy	Prior steroid therapy	Prior radiation therapy	Total cases
Objective responses	7 (50 %)	3 (21 %)	1 (7 %)	–	1 (7 %)	–	1 (7 %)	1 (7 %)	14
Subjective responses	18 (40 %)	17 (38 %)	5 (11 %)	1 (2 %)	–	3 (7 %)	–	1 (2 %)	45

with either weight gain or a cessation of weight loss. 48 (81 %) showed an improvement in performance status as measured by an increase in strength, bulation or both. And 21 (36 %) showed a decrease in pain as measured by a inuted need for analgesics.

Ongoing concurrent (or prior) anticancer therapy. Various of the improved cases were treated with either steroids and/or cytotoxic chemotherapy and/or radiation, prior to initiation of hydrazine sulfate therapy, as indicated in table III. In all these cases the noted improvements occurred *after* the addition of hydrazine sulfate to the therapy. In regard to the objective responses 7 (50 %) of the 14 cases were treated with hydrazine sulfate alone, without concurrent or prior anticancer therapy of any type, while 7 (50 %) of the cases did receive concurrent or prior anticancer therapy. In the subjective-only responses, 18/45 or 40 % of the cases were treated only with hydrazine sulfate, without concurrent or prior anticancer therapy, while 27 of the cases (60 %) did receive concurrent or prior anticancer therapy.

'No Improvements'

Of the 25 'no improvement' cases 2 (8 %) expired within 3–4 weeks after initiation of hydrazine sulfate therapy; 2 (8 %) had very little information in their Patient Report Form so that actual categorization became difficult; 9 (36 %) had a drug trial of only 3–4 weeks, and 14 (56 %) had concurrent anticancer therapy which consisted of cytotoxic drugs, radiation, steroids or combinations thereof. *In only 5 cases* were these foregoing considerations not a factor, i.e., the patient had an adequate prognosis and drug trial, had no concurrent or prior anticancer therapy, and had sufficient information submitted on his Patient Report Form to support a categorization of 'no improvement'.

Nonevaluable Cases

The general breakdown of categories of the 74 nonevaluable cases is given above and in table II. Of a total of 31 of these cases excluded from evaluation because of inadequate prognosis (survival time), 11 died within 1 week of initiation of hydrazine sulfate therapy, 22 died within 2 weeks, and the full 31 died within 3 weeks. Of a total of 25 additional cases excluded from evaluation for reasons of inadequate drug trial, 8 were on drug for only 1 week or less, 14 were on drug for 2 weeks or less, and the full 25 were on drug for 3 weeks or less. Thus, of the 56 cases excluded from consideration for the foregoing two reasons, 19 had a survival time or drug trial of 1 week or less, 36 had a survival time or drug trial of 2 weeks or less, and the full number – 56 – had a survival time or drug trial of 3 weeks or less.

Side Effects

Side effects were determined on the basis of evaluable cases only and were in general mild. They comprised: *extremity paresthesias* (5 %); this condition was diminished or eliminated by a reduction of dosage and/or administration of pyridoxine hydrochloride (vitamin B_6) in excess of 25 mg daily; *nausea* (4 %), in most cases transient; nontransient nausea was eliminated by a reduction of dosage or withdrawal of medication for a period of several days, then reinstitution of treatment at lower dosage levels; *dry skin* or *transient pruritis* (3 %); *'dizziness'* (1 %); *'drowsiness'* (1 %); *possible thrombophlebitis* (1 %) (it was not known whether this condition was drug-related). The total evaluable cases showing side effects numbered 13/84 or an overall 15 %. There were no deaths attributable to hydrazine sulfate therapy, either in the evaluable or in the nonevaluable cases.

Discussion

It is important that a detailed analysis of a study of this nature include not only the obviously improved cases as a result of hydrazine sulfate administration, but also the nonimproved and nonevaluable cases. Such factors as poor patient and clinician selection as well as inadequate protocol planning, must be assessed as to their quantitative contribution to the latter two categories.

Nonimproved and Nonevaluable Cases

Lack of proper patient selection, via inadequate patient prognosis and inadequate drug trial, contributed heavily to the large number of nonevaluable and nonimproved cases. Minimum protocol-recommended prognosis was 2 months, yet as many as 31/74 or 42 % of the nonevaluable cases were so designated because of a survival time of 3 weeks or less, while in the nonimproved category

2/25 or 8 % of the cases had a survival time of only 3–4 weeks. In addition, as many as 25/74 or 34 % of the nonevaluable cases were so designated because of an inadequate drug trial (3 weeks or less), while 9/25 or 36 % of the nonimproved cases had a drug trial of only 3–4 weeks. Thus, in the nonevaluable category the number of combined inadequate prognosis and inadequate drug trial cases totaled 56/74 or 76 %, while in the nonimproved category the number of combined cases of 'borderline-acceptable' survival time and drug trial (3–4 weeks) totaled 11/25 or 44 %. Such large percentages, representing inadequate prognosis and inadequate drug trial, must be attributed chiefly to improper patient selection and not to the occasional misevaluations which arise in any study.

Lack of proper clinician selection was also an apparent factor in this study, manifest chiefly in those cases in which too little information was submitted. In the nonevaluable category as many as 15/74 or 20 % of the cases were so designated because of lack of sufficient information upon which to make an evaluation. Even in the nonimproved category 2/25 or 8 % of the cases had only a minimum of information submitted. Such numbers surely reflect a lack of interest or capability on the part of the clinician. (Indeed, inadequate patient selection itself may be a function of this type of clinician inadequacy.)

Poor protocol planning, manifest by the acceptability of concurrent anticancer therapy, also had a major input in these two categories. In the nonevaluable group 3/74 or 4 % of the cases were so designated because of newly initiated concurrent cytotoxic chemotherapy, rendering impossible any attributive evaluation of patient response. In the nonimproved group as many as 14/25 or 56 % of the cases had ongoing concurrent anticancer therapy which was no longer producing demonstrable clinical benefit, but which could, by virtue of its immunosuppressive and hematosuppressive effects, adversely affect or mask the results of any new drug concurrently administered. Clearly, the protocol was weakened by inclusion of any type of concurrent anticancer therapy whatsoever.

Thus, in retrospect many of the cases which fell into the nonevaluable and nonimproved categories should properly never have entered this study. This circumstance could have been obviated by better patient and clinician selection as well as by a 'tighter' protocol. It is hoped that a careful categorization in this study has dealt adequately with these factors.

Improved Cases

Despite the above-described considerations, a large number of clearly improved cases emerged in this study. This improvement, moreover, was the result of administration of hydrazine sulfate alone in a large percentage of the cases and was not influenced by any other mode of concurrent or prior anticancer therapy. Table III indicates that 50 % of the objectively improved cases (7/14) were on hydrazine sulfate alone, with no prior or concurrent anticancer therapy;

and 40 % (18/45) of the subjective-only responses were also the result of hydrazine sulfate therapy alone. This constitutes strong *prima faciae* evidence indicating hydrazine sulfate to be a clinically active anticancer agent in itself. It is important to remember that even in those cases which received concurrent or prior anticancer therapy, the noted improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Thus, whether as a sole agent or in combination with other agents, administration of hydrazine sulfate to advanced cancer patients is linked to marked anticancer responses.

Moreover, hydrazine sulfate is apparently not a 'tumor-specific' agent, as can be seen from table I. Virtually all types of cancer – especially those which ultimately promote a degree of host cachexia – are apparently susceptible to its actions. Reports, in addition to those of this study, which have reached this laboratory, indicate that the spectrum of disease beneficially affected by hydrazine sulfate extends to cancers arising from all organ systems and/or tissues in the body. The most dramatic responses reported to date have been those with primary lung neoplasms, although this observation may prove to be premature as more and earlier cases are reported.

The duration of improvement has been unpredictable, but has generally been longer in those cases responding objectively (as well as subjectively). Some of the responses have been of very short duration. But others have been quite lengthy. To date three cases in this study – two primary lung and one ovarian – are alive 17, 18 and 21 months after institution of hydrazine sulfate therapy alone, respectively; all three were previously considered terminal or preterminal. Preliminary indications suggest that the improvements brought about hy hydrazine sulfate therapy – whether objective or subjective – have been accompanied by extension in survival time and that the quality of this survival time was high: patients who had obtained objective response and/or increased appetite, strength and decreased pain as a result of hydrazine sulfate therapy, were reported to have been restored to a more positive orientation toward living.

The duration of improvement may also be related to the degree of advancement of the disease. The patients in this study were in general in the very latest stages of disease, yet there were many improvements, some of which were marked. However, it is generally regarded that any modality of anticancer therapy has its best chances of success when used *early* in the course of disease. And this is probably true of hydrazine sulfate. There would seemingly be no disadvantage in instituting hydrazine sulfate therapy early in the course of disease, especially in those cases where the ultimate clinical course is virtually unaffected by any known therapeutic modality. Moreover, since the toxicity of hydrazine sulfate is apparently of a low order of magnitude, unlike many of the cytotoxic drugs whose 'side effects' can produce extreme patient discomfort and death, it would seem prudent to investigate the effect of this drug on early patients, rather than use it at the very last stages as a 'resurrective' type of therapy. If

positive responses can be obtained in terminal patients – as indicated in this study – it seems only reasonable that a greater degree of positive response could be expected in early patients, as is the case with many other anticancer modalities.

Side Effects

The side effects of hydrazine sulfate are indeed of a very minor nature as reported in this study, with the possible exception of 'torpidity' or 'drowsiness' which had less than a 1 % incidence and occurred only in very advanced bedridden case(s). The most frequent side effect, occurring usually after the 6th week of therapy, appears to be the development of mild extremity paresthesias, particularly of the fingers and toes. This condition reportedly can be diminished or eliminated by dosage reduction and/or addition of vitamin B_6 (in excess of 25 mg daily) to the regimen. Other side effects such as nausea, pruritis, etc., appear to be transient in nature and not a clinical problem, with few exceptions. In general, since hydrazine sulfate is not a cytotoxic agent, there have been none of the severe side effects of these drugs reported with its use, and this is especially true of hematopoietic-suppressive effects. Hydrazine sulfate does not depress the bone marrow. On the contrary, several of the cases of this study with advanced prostatic or breast cancer showed net *elevations* in hemoglobin, hematocrit and platelets within 2 weeks of initiation of treatment. This observation has been confirmed in many case reports not a part of this study and thus is in contrast to the cytotoxic drugs, one of the prime limitations of which are their hematosuppressive effects. Finally, hydrazine sulfate has not been demonstrated clinically to possess immunosuppressive properties, although this must await verification by further basic studies.

Concluding Remark

Hydrazine sulfate therapy is a new type of chemotherapy. Its clinical use at present represents a *beginning*. Whether a study with any new drug is positive or negative, it must always be evaluated in terms of the 'state of the art'. Hydrazine sulfate represents the *first* of a class of new agents designed to interrupt host participation in cancer. Other agents in this class now in development may prove to be far superior to hydrazine sulfate. In addition, adjunctive agents to hydrazine sulfate therapy may also prove to be very important. In this respect it has already been learned by this laboratory that administration of a substance interfering with triglyceride synthesis, can greatly potentiate the anticancer action of hydrazine sulfate (paper in preparation). For these types of reasons it must be emphasized that the clinical potential of hydrazine sulfate-like drugs in cancer has only just begun to be explored, and much further work lies ahead before a more comprehensive understanding of their ultimate anticancer potential becomes clear.

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Oncology *32:* 11–20 (197

Primary C-Cell Hype

Mirosław Beskid

Laboratory of Histochemis
Postgraduate Medical Educ

Key Words. Thyroid C cells
carcinoma

Abstract. The electron mi
C-cell hyperplasia in 'hot' thyroid
was found within nodule tissue.
in normal thyroid tissue plays

Introduction

It was demonstrated on
methods that the so-called p
the follicular cells and cons
gland (2, 6, 8, 19, 21, 29,
exclusively restricted to neop
and pathological properties (
(1, 3, 9, 23–27, 31, 35, 36)
recently described C-cell ad
besides neoplasm the C cells
hyperplasia within normal th

Owing to the fact that
hyperplasia preceding carcin
microscopic properties of C
such a case seems relevant.

A. INGREDIENT NAME:

IODOFORM

B. Chemical Name:

Tri-iodomethane

C. Common Name:

Compound Iodoform Paint, B.I.P.P. Gauze, Bismuth Sub-nitrate and Iodoform Paste

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay:	99.0-100.5%	99.01%

Not less than 99% of CHI_3

E. Information about how the ingredient is supplied:

Fine greenish yellow powder, or lustrous crystals, unctuous touch, characteristic. Persistent odor, slightly volatile evenm at ordinary temperatures, and distils slowly with steam.

F. Information about recognition of the substance in foreign pharmacopeias:

British Pharmacopeia 1954
The National Formulary - Volume VII, 1942

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Corbridge, R. J., Djazaeri, B., and Hellier, W. P. Iodoform Paste. *Clinical Otolaryngology,* 1995; 20(4): 305-307.

Holan, G. and Fuks, A. B. Iodoform-containing paste (KRI). *Pediatric Dentistry,* 1993; 16(6): 403-407.

H. Information about dosage forms used:

Paste
Paint
Gauze

I. Information about strength:

10-50% Topically

J. Information about route of administration:

Topically

K. Stability data:

Decomposition at about 120°; decomposition at high temperature with evolution of iodine.
Decomposes violently at 400F

L. Formulations:

M. Miscellaneous Information:

50-1127
52738

CERTIFICATE OF ANALYSIS

PRODUCT: IODOFORM POWDER
RELEASE #: N

LOT # :B59901C13

GRADE: PURIFIED
CODE:A925D053

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	YELLOW POWDER	CONFORMS
2.	Melting point	115 deg C min.	120 deg C
3.	Moisture	1.0% max.	< 1.0%
4.	Residue on ignition	0.2% max.	< 0.2%
5.	Assay	~~99.0 - 100.5%~~	99.01% D

ATTENTION: TONY HATCHETT

Date :09/02/97 Prepared by : A. HAZARI

10540 Approved by :

Our Order # 237082 Your PO # 53617

QUALITY CONTROL REPORT

CHEMICAL NAME.: IODOFORM PURIFIED _____

MANUFACTURE LOT NO.: B62949P30

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
E YELLOW POWDER OR CRYSTALS; UNCTUOUS TOUCH; CHARACTERISTIC, DISAGREEABLE ODOR.

2) SOLUBILITY.:
VERY SLIGHTLY SOLUBLE IN WATER; 1 GRAM DISSOLVES IN 60ML COLD ALCOHOL, 16ML BOILING ALCOHOL, 10ML CHLOROFORM, 7.5ML ETHER, 80ML IN GLYCEROL; FREELY SOLUBLE IN BENZENE, ACETONE.

3) MELTING POINT.:
K MELTS AT ABOUT 120 DEGREES; DECOMPOSITION AT HIGH TEMPERATURE WITH EVOLUTION OF IODINE.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

Iodoform, 99+%
97101

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Iodoform, 99+%

```
     Triiodomethane
Company Identification:  Acros Organics N.V.
                         One Reagent Lane
                         Fairlawn, NJ  07410
For information in North America, call:   800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300
For emergencies in the US, call CHEMTREC: 800-424-9300
```

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
75-47-8	Iodoform, 99+%		200-874-5

Hazard Symbols: XN
Risk Phrases: 20/21/22

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: Not available.
Cancer suspect agent.
Target Organs: None.

Potential Health Effects

The toxicological properties of this material have not been investigated. Use appropriate procedures to prevent opportunities for direct contact with the skin or eyes and to prevent inhalation.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:

Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids.

Skin:

Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:

Do NOT induce vomiting. Allow the victim to rinse his mouth and then to drink 2-4 cupfuls of water, and seek medical advice.

Inhalation:
Remove from exposure to fresh air immediately.

Notes to Physician:
Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion.

Extinguishing Media:
Use agent most appropriate to extinguish fire.

Autoignition Temperature: Not available.
Flash Point: 204 deg C (399.20 deg F)
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:
Clean up spills immediately, observing precautions in the Protective Equipment section. Sweep up, then place into a suitable container for disposal.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Avoid contact with eyes, skin, and clothing. Avoid ingestion and inhalation.

Storage:
Store in a cool, dry place. Keep container closed when not in use.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
Use adequate general or local exhaust ventilation to keep airborne concentrations below the permissible exposure limits. Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
Iodoform, 99+%	0.6 ppm ; 10 mg/m3	none listed	none listed

OSHA Vacated PELs:
Iodoform, 99+%:
0.6 ppm TWA; 10 mg/m3 TWA

Personal Protective Equipment

Eyes:
Wear safety glasses and chemical goggles if splashing is possible.

Skin:
Wear appropriate protective gloves and clothing to prevent skin exposure.

Clothing:
Wear appropriate protective clothing to minimize contact with skin.

Respirators:
Wear a NIOSH/MSHA-approved (or equivalent) full-facepiece airline respirator in the positive pressure mode with emergency escape provisions.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Not available.
Appearance:	Not available.
Odor:	None reported.
pH:	Not available.
Vapor Pressure:	Not available.
Vapor Density:	Not available.
Evaporation Rate:	Not available.
Viscosity:	Not available.
Boiling Point:	@ 760.00mm Hg
Freezing/Melting Point:	120.00 - 123.00 deg C
Decomposition Temperature:	204 deg C
Solubility:	freely soluble in benzene and acetone
Specific Gravity/Density:	4.0080g/cm3
Molecular Formula:	CHI3
Molecular Weight:	393.72

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
Stable under normal temperatures and pressures.
Conditions to Avoid:
Incompatible materials, strong oxidants.
Incompatibilities with Other Materials:
Strong bases - strong oxidizing agents - magnesium - alkali metals.
Hazardous Decomposition Products:
Carbon monoxide, irritating and toxic fumes and gases, carbon dioxide, hydrogen iodide.
Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 75-47-8: PB7000000
LD50/LC50:
CAS# 75-47-8: Inhalation, rat: LC50 =165 ppm/7H; Oral, mouse: LD50 = 470 mg/kg; Oral, rabbit: LD50 = 450 mg/kg; Oral, rat: LD50 = 355 mg/kg; Skin, rat: LD50 = 1184 mg/kg.
Carcinogenicity:
Iodoform, 99+% -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.
RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
No information available
IMO
Not regulated as a hazardous material.
IATA
Not regulated as a hazardous material.

RID/ADR
Not regulated as a hazardous material.
Canadian TDG
No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL
TSCA
CAS# 75-47-8 is listed on the TSCA inventory.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b
None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.
SARA
Section 302 (RQ)
None of the chemicals in this material have an RQ.
Section 302 (TPQ)
None of the chemicals in this product have a TPQ.
SARA Codes
CAS # 75-47-8: acute, chronic.
Section 313
No chemicals are reportable under Section 313.
Clean Air Act:
This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.
Clean Water Act:
None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.
OSHA:
None of the chemicals in this product are considered highly hazardous by OSHA.
STATE
Iodoform, 99+% can be found on the following state right to know lists: California, New Jersey, Florida, Pennsylvania, Minnesota, Massachusetts.
California No Significant Risk Level:
None of the chemicals in this product are listed.
European/International Regulations
European Labeling in Accordance with EC Directives
Hazard Symbols: XN
Risk Phrases:
R 20/21/22 Harmful by inhalation, in contact with skin and if swallowed.
Safety Phrases:
S 24/25 Avoid contact with skin and eyes.
WGK (Water Danger/Protection)
CAS# 75-47-8:
Canada
CAS# 75-47-8 is listed on Canada's DSL/NDSL List.
This product has a WHMIS classification of D1B, D2B.
CAS# 75-47-8 is not listed on Canada's Ingredient Disclosure List.
Exposure Limits
CAS# 75-47-8:. OEL-AUSTRALIA:TWA 0.6 ppm (10 mg/m3). OEL-BELGIUM:TWA 0.6 ppm (10 mg/m3). OEL-DENMARK:TWA 0.2 ppm (3 mg/m3). OEL-FINLAND:TWA 0.2 ppm (3 mg/m3);STEL 0.6 ppm (1 mg/m3);Skin. OEL-FRANCE:TWA 0.6 ppm (10 mg/m3). OEL-THE NETHERLANDS:TWA 0.2 ppm (3 mg/m3). OEL-SWITZERLAND:TWA 0.6 ppm (10 mg/m3). OEL-UNITED KINGDOM:TWA 0.6 ppm (10 mg/m3);STEL 1 ppm (20 mg/m3). OEL IN BULGARIA, COLOMBIA, JORDAN, KOREA check ACGIH TLV. OEL IN NEW ZEALAND, SINGAPORE, VIETNAM check ACGI TLV

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 2/01/1996 Revision #0 Date: Original.

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Back to product information.

phosphorous acid, H_3PO_2, added to prevent discoloration on keeping. Wt per ml about 1.1 g. **Incompatible** with alkalis and oxidising agents. **Store** in well-closed glass-stoppered bottles. Protect from light.

The hydriodic acid has the general properties of one in weak combination. It was usually administered as Hydriodic Acid Syrup.

Preparations

Hydriodic Acid Syrup *(B.P.C. 1949).* Syr. Acid. Hydriod. Dilute hydriodic acid 10 ml, water 5 ml, and syrup to 100 ml. *Dose.* 2 to 4 ml.

4576-k

Iodinated Glycerol. Iodopropylidene Glycerol. An isomeric mixture of iodinated dimers of glycerol, $C_6H_{11}IO_3 = 258.1$. It contains about 50% of organically bound iodine.

CAS — 5634-39-9.

A pale yellow liquid with a pungent bitter after-taste. **Soluble** in chloroform, ether, and ethyl acetate. **Protect** from light.

Adverse Effects, Treatment, and Precautions. As for Iodine, p.862.

Uses. Iodinated glycerol is used as an expectorant in bronchitis and bronchial asthma in doses of 60 mg four times daily with fluids.

Proprietary Preparations

Organidin *(WB Pharmaceuticals, UK: Boehringer Ingelheim, UK).* Elixir containing in each 5 ml iodinated glycerol 60 mg and alcohol 1.25 ml (suggested diluent, equal parts of glycerol and water).

Other Proprietary Names

Mucorama Rectal Infantil *(Spain).*

4577-a

Iodoform *(B.P.C. 1954).* Formène Tri-iodé. Iodomethane. $CHI_3 = 393.7$.

CAS — 75-47-8.

Pharmacopoeias. In *Arg., Aust., Belg., Fr., It., Jug., Pol., Port., Rus., Span.,* and *Swiss.*

Shining lemon-yellow crystals or powder, somewhat unctuous to the touch, with a characteristic, persistent, penetrating odour and disagreeable taste. Slightly volatile at room temperature. M.p. 115°; at higher temperatures it decomposes with loss of iodine.

Practically **insoluble** in water; soluble 1 in 60 of alcohol, 1 in 3 of carbon disulphide, 1 in 13 of chloroform, 1 in 8 of ether, 1 in 100 of glycerol, 1 in 35 of olive oil; soluble in other fixed and volatile oils, and in flexible collodion. **Incompatible** with alkalis, oxidising agents, lead, silver, and mercury salts. **Store** in a cool place in airtight containers. Protect from light.

To cover its odour it may be mixed with coumarin 1 in 50, or with menthol, phenol, or thymol, or with oils of anise, eucalyptus, geranium, peppermint, rosemary, or sassafras, about 1 or 2%.

Adverse Effects. Symptoms of systemic toxicity, as described under Iodine (see p.862), sometimes occur on prolonged or extensive application to wounds. As a precaution not more than 2 g should usually be applied as a wound dressing. Some persons are hypersensitive to iodoform and even small quantities applied locally may cause an erythematous rash.

Severe poisoning, which may be fatal, is characterised by headache, somnolence, delirium, and rapid feeble pulse.

Maximum permissible atmospheric concentration 6 ppm.

Uses. Iodoform has a marked anaesthetic action when applied to mucous membranes. It slowly releases elemental iodine when applied to the tissues and has a mild disinfectant action. It was formerly used extensively as a wound dressing but is not very effective.

Compound Iodoform Paint has been used as a protective covering and to hold gauze dressings and radium needles in position.

Bismuth Subnitrate and Iodoform Paste (BIPP) has been applied to wounds and abscesses, the area to be treated being cleaned and smeared with the paste. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Preparations

B.I.P.P. Gauze *(Roy. Nat. T. N. and E. Hosp.).* Sterile ribbon gauze impregnated with a sterile paste consisting of iodoform 40%, bismuth subnitrate 20%, and liquid paraffin 40%.

Bismuth Subnitrate and Iodoform Paste *(B.P.C. 1954).* Past. Bism. Subnit. et Iodof.; BIPP; Bismuth and Iodoform Paste. Bismuth subnitrate 1, iodoform 2, sterilised liquid paraffin 1, by wt, prepared aseptically. Store in a cool place in sterilised collapsible tubes. Prolonged or extensive application may give rise to iodoform poisoning.

Adverse effects. Open leg ulcers in a Malay child aged 13 months were treated with the paste. They healed but oedema and pain increased. After 9 weeks, X-ray examination showed dense transverse bands of metallic bismuth deposited in metaphyseal growth areas of long bones.— H. N. Krige, *S. Afr. med. J.*, 1963, *37*, 1005.

Two reactions to dental dressings with Bismuth Subnitrate and Iodoform Paste occurred in which crystals of bismuth subnitrate were considered to be the cause rather than the iodoform.— W. A. Miller and G. S. Taylor, *Br. dent. J.*, 1968, *124*, 420.

Symptoms compatible with iodoform toxicity occurred in 1 patient and raised iodine concentrations in 2 further patients following the packing of cavities with gauze impregnated with Bismuth Subnitrate and Iodoform Paste. In a further patient who received a pack soaked in Compound Iodoform Paint no signs of iodoform toxicity were observed. It was suggested that Bismuth Subnitrate and Iodoform Paste was satisfactory for packing small operative cavities but for large cavities Compound Iodoform Paint pastes were safer.— A. F. F. O'Connor *et al., J. Lar. Otol.*, 1977, *91*, 903.

Compound Iodoform Paint *(B.P.C. 1954).* Pig. Iodof. Co.; Iodoform Varnish; Whitehead's Varnish. Prepared from iodoform 10 g, benzoin 10 g, prepared storax 7.5 g, tolu balsam 5 g, and solvent ether to 100 ml.

4578-t

Iodophores

Iodophores are carriers of iodine and are usually complexes of iodine with certain types of surfactants with detergent properties. It is possible for iodine to be taken up in chemical combination by high molecular weight surfactants and water-soluble polymers. The surfactants may be nonionic, cationic, or anionic, but generally the most efficient and stable iodophores are compounds of nonionic surfactants.

Though the iodine in an iodophore is held in loose chemical combination, part of the iodine is available and retains its bactericidal activity. Iodophores may solubilise up to 25% by weight of iodine of which about 80% may be released as available iodine when a concentrated solution is diluted.

Solutions of an iodophore are more stable than solutions of iodine which lose strength by volatilisation and there is no precipitation on dilution of an iodophore solution. The stability of the majority is not affected by changes in pH. As the available iodine is taken up, the colour of the solution changes from amber to pale yellow.

Unlike the hypochlorites, solutions of iodophores can be formulated with acid and the bactericidal action of most of them is enhanced by lowering the pH. Increases in temperature increase the bactericidal action of iodophores, but above 43° they break down with the liberation of iodine.

Stability of solutions. Use-dilutions of an iodophore preparation (Wescodyne) containing 150 ppm available iodine and 0.05% sodium nitrite lost their typical brown colour after standing for a few days and were found to lose 24% potency in 24 hours or 42% in 48 hours at 35°. Similar dilutions without sodium nitrite were more stable and lost 9.2% potency after 3 weeks at 35°.— R. J. Abrahams and H. J. Derewicz, *Am. J. Hosp. Pharm.*, 1968, *25*, 192.

Uses. Solutions of iodophores are employed in pre-operative skin disinfection and for disinfecting blankets and some instruments. Stains of iodophores on skin and natural fabrics may be removed by washing with soap and water. The iodophores described in this section are Povidone-Iodine (see p.867) and Undecoylium Chloride-Iodine (see p.868).

Disinfection of skin. There was no significant difference in the incidence of wound infections when an iodophore and hexachlorophane were used as surgical hand scrubs.— J. J. White and A. Duncan, *Surgery Gynec. Obstet.*, 1972, *135*, 890.

The effectiveness of iodophores against both Gram-negative and Gram-positive organisms was an advantage over hexachlorophane, but they did not persist in the skin to provide cumulative, continuing antibacterial activity. Like alcohol, iodophores could cause excessive dryness of the skin with repeated use.— *Med. Lett.*, 1976, *18*, 85. Iodophores were active against both Gram-negative and Gram-positive bacteria and did not require repeated application for maximum effectiveness. They were considered to be less bactericidal but less irritant than aqueous or alcoholic solutions of iodine.— *ibid.*, 1977, *19*, 83.

Studies involving 95 women in active labour necessitating continuous epidural analgesia indicated that skin disinfection of the catheter site with an iodophore (Prepodyne) was superior to that with a benzalkonium chloride preparation.— E. Abouleish *et al., Anesthesiology*, 1977, *46*, 351.

For other reports, see Povidone-Iodine, p.867.

Uses of disinfectants on farms. For a list of disinfectants, including iodophores, and their rate of dilution approved for use in Great Britain in foot-and-mouth disease, swine vesicular disease, fowl pest, and tuberculosis in animals, see The Diseases of Animals (Approved Disinfectants) Order 1978 (SI 1978: No. 32), as amended (SI 1978: No. 934; SI 1979: No. 37).

A list of proprietary iodophore preparations approved for the cleansing and disinfecting of milk containers and appliances is contained in Circular FSH 8/78, Ministry of Agriculture, Fisheries and Foods, London, HM Stationery Office, 1978.

Virus disinfection. For the disinfection of materials in contact with lassa fever virus, see *Memorandum on Lassa Fever*, Dept of Health and Social Security, London, HM Stationery Office, 1976.

Recommendations for precautions in medical care of, and in handling materials from, patients with transmissible virus dementia (Creutzfeldt-Jakob disease).— D. C. Gajdusek *et al., New Engl. J. Med.*, 1977, *297*, 1253.

For the use of iodophores in the disinfection of fabrics exposed to smallpox virus, see Disinfectants, General, p.548.

Proprietary Preparations

Faringets *(Winthrop, UK).* Lozenges each containing 4 mg of miristalkonium iodine chloride (myristyl benzalkonium iodine chloride; benzyldimethyltetradecylammonium chloride-iodine complex; $C_{23}H_{42}ClI_2N = 621.9$). For minor infections of the throat. *Dose.* 1 or 2 lozenges to be sucked slowly every 4 hours; not more than 6 in 24 hours.

Steribath *(Stuart, UK).* An antiseptic solution containing an iodophore (complexed with a nonoxynol) and providing 4.5% of available iodine; available in 14-ml sachets for addition to the bath.

Vanodine *(Evans Vanodine, UK).* A bactericidal and fungicidal detergent solution containing available iodine 1.92% w/v (in the form of an iodine-poloxamer complex 18.7%). For the control of foot infections in swimming baths and changing rooms. Dilute 1 vol. in 100 vol. of water for use.

Other Proprietary Names

SeptoDyne *(USA).*

X 1955

mixture vigorously. After the chloroform has been decolorized allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each ml. of 0.05 *M* potassium iodate is equivalent to 30.55 mg. of iodochlorhydroxyquin (C_9H_5ClINO).

Tablets available—Iodochlorhydroxyquin Tablets usually available contain the following amount of iodochlorhydroxyquin: 250 mg. (4 grains).

Packaging and storage—Preserve Iodochlorhydroxyquin Tablets in tight, light-resistant containers.

CATEGORY—Antiprotozoan.

USUAL DOSE OF IODOCHLORHYDROXYQUIN—**250 mg.** (approximately 4 grains).

Iodoform

IODOFORM

Triiodomethane

CHI_3 Mol. wt. 393.75

Iodoform, previously dried over sulfuric acid for 4 hours, contains not less than 99 per cent of CHI_3.

Description—Iodoform occurs as a fine greenish yellow powder, or lustrous crystals. It has a peculiar, very penetrating, persistent odor. Iodoform is slightly volatile even at ordinary temperatures, and distils slowly with steam.

Solubility—One Gm. of Iodoform dissolves in about 60 ml. of alcohol, in about 80 ml. of glycerin, in about 10 ml. of chloroform, in about 7.5 ml. of ether, and in about 34 ml. of olive oil. One Gm. dissolves in about 16 ml. of boiling alcohol. Iodoform is practically insoluble in water to which, however, it imparts its odor and taste.

Melting point—Iodoform melts to a brown liquid at about 115°, and decomposes at a higher temperature, emitting vapors of iodine, page 691.

Loss on drying—Dry Iodoform over sulfuric acid for 4 hours: it loses not more than 1 per cent of its weight, page 690.

Residue on ignition—Iodoform yields not more than 0.2 per cent of residue on ignition, page 711.

Coloring matter, acids, and alkalies—Shake about 2 Gm. of Iodoform with 5 ml. of water for 1 minute, and filter: the filtrate is colorless and free from bitter taste and is neutral to litmus.

Assay—Dissolve about 200 mg. of Iodoform, previously dried over sulfuric acid for 4 hours and accurately weighed, in 20 ml. of alcohol in a 500-ml. glass-stoppered Erlenmeyer flask. Add 30 ml. of 0.1 *N* silver nitrate and 10 ml. of nitric acid, stopper the flask, and set it aside overnight. Add 150 ml. of water and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess of silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 13.12 mg. of CHI_3.

Packaging and storage—Preserve Iodoform in tight, light-resistant containers, and avoid excessive heat.

CATEGORY—Local antibacterial.

IPECAC AN

Dover's Powder

Ipecac, in very fine powder . . .
Powdered Opium . . . . . .
Lactose, coarsely powdered . . .
To make .

Triturate the ingredients reduced to a very fine, unifor

Description—Ipecac and Opium P hibiting coarse, angular, frequer up to 400 μ in length, very slowly polarizing light with a strong disp of identification are the tissues described in the U. S. Pharmacc

Packaging and storage—Preserve ers.

CATEGORY—Diaphoretic.

USUAL DOSE—**300 mg.** (ap

One usual metric dose contains

Orizaba Jalap

Ipomea is the dried root c *volvulaceæ*).

Ipomea yields not less tha

Unground Ipomea occurs as nearl diameter, and from 1 to 5.5 cm wrinkled, and has a tough, fib rings with protruding lighte crushed has a distinct, somewha what acrid.

Histology—Ipomea shows a corky cells; an outer cortex of severa made up of thick-walled, tanger or crystals of calcium oxalate, to yellow resinous latex; rings alternating with bands of pare outside of the wood-wedges. numerous and distributed thro surrounding the bundles are r calcium oxalate crystals.

Powdered Ipomea is pale brown up to 35 μ in diameter, mostly

Extract the mixed drugs by percolation, using diluted alcohol as the menstruum. Macerate three hours, and percolate at a moderate rate until 250 cc. of percolate is obtained. To this add sufficient distilled water to make the product measure 1000 cc.; or, to prepare the Infusion in smaller quantities and extemporaneously, add sufficient distilled water to 1 volume of the percolate to make 4 volumes of the Infusion.

NOTE: The percolate or concentrated infusion may be preserved in tight containers, but the Infusion must not be dispensed unless it has been recently prepared.

Storage—Dispense Compound Infusion of Gentian in tight containers.
Alcohol content—From 9 to 11 per cent, by volume, of C_2H_5OH.

AVERAGE DOSE—Metric, 15 cc.; Apothecaries, 4 fluidrachms.

INFUSUM SENNÆ CUM MAGNESII SULFATE
Infusion of Senna with Magnesium Sulfate

Inf. Senn. c. Mag. Sulf. Compound Infusion of Senna

Senna	60 Gm.
Manna	120 Gm.
Magnesium Sulfate	120 Gm.
Fennel, bruised	20 Gm.
Distilled Water, a sufficient quantity,	
To make	1000 cc.

Pour 800 cc. of boiling distilled water upon the senna, manna, and fennel, contained in a suitable vessel, and allow the mixture to infuse for half an hour, pass the liquid through a strainer and express the marc. Dissolve the magnesium sulfate in the liquid, and add sufficient distilled water through the strainer to make the Infusion measure 1000 cc. Filter if necessary, until the product is clear.

NOTE: This preparation must not be dispensed unless it has been recently prepared.

Storage—Dispense Infusion of Senna with Magnesium Sulfate in tight containers.

AVERAGE DOSE—Metric, 60 cc.; Apothecaries, 2 fluidounces.

IODOFORMUM
Iodoform

Iodof. Triiodomethane

Iodoform, previously dried over sulfuric acid for 24 hours, contains not less than 99 per cent of CHI_3 (393.78).

Description—Iodoform occurs as a fine lemon-yellow powder, or lustrous crystals. It has a peculiar, very penetrating, persistent odor. Iodoform is slightly volatile even at ordinary temperatures, and distils slowly with the vapor of water.
Solubility—Iodoform is practically insoluble in water to which, however, it imparts its odor and taste. One Gm. of Iodoform dissolves in about 60 cc. of alcohol, in about 80 cc. of glycerin, in about 10 cc. of chloroform, in about 7.5 cc. of ether, and in about 34 cc. of olive oil, at 25° C. One Gm. dissolves in about 16 cc. of boiling alcohol.
Melting point—Iodoform melts to a brown liquid at about 115° C., and decomposes at a higher temperature, emitting vapors of iodine.
Loss on drying—One Gm. of Iodoform dried over sulfuric acid for 24 hours loses not more than 1 per cent of its weight.
Ash—Iodoform yields not more than 0.2 per cent of ash upon ignition.
Coloring matter, acids, and alkalies—Shake about 2 Gm. of Iodoform with 5 cc. of distilled water for one minute, and filter: the filtrate is colorless and free from bitter taste and is neutral to litmus paper.
Assay—Dissolve about 0.2 Gm. of Iodoform, previously dried over sulfuric acid for 24 hours and accurately weighed, in 20 cc. of alcohol in a 500 cc. glass-stoppered Erlenmeyer flask. Add 30 cc. of tenth-normal silver nitrate and 10 cc. of nitric acid, stopper the flask, and set it aside overnight. Add 150 cc. of distilled water and 5 cc. of ferric ammonium sulfate T.S., and titrate the excess of silver nitrate with tenth-normal ammonium thiocyanate. Each cc. of tenth-normal silver nitrate is equivalent to 0.01313 Gm. of CHI_3.
Storage—Preserve Iodoform in tight containers, protected from light, and avoid excessive heat.

IPOMŒA
Ipomea

Ipom. Orizaba Jalap Mexican Scammony

Ipomea is the dried root of *Ipomœa orizabensis* Ledenois (Fam. *Convolvulaceæ*).

Ipomea yields not less than 15 per cent of the total resins of Ipomea and not more than 3 per cent of acid-insoluble ash.

Unground Ipomea—Nearly flat transverse slices, from 2 to 12 cm. in diameter, and from 1 to 5.5 cm. in thickness; externally brown, very deeply wrinkled; fracture tough, fibrous; cut surface showing concentric rings with protruding lighter-colored fibro-vascular bundles.
Histology—A corky layer of several rows of thin-walled, narrow, tabular cells; outer cortex of several layers of thin-walled cells; a broad cortical layer made up of thick-walled, tangentially elongated cells, containing either starch grains or crystals of calcium oxalate, and numerous large cells containing reddish brown to yellow resinous latex; rings or zones of small collateral fibro-vascular bundles, alternating with bands of parenchyma; sieve in semi-cylindrical strands outside of the wood wedges; medullary rays broad; resin cells numerous and distributed throughout the parenchyma; the parenchyma cells surrounding the bundles, more or less collapsed and containing either starch or calcium oxalate crystals.
Powdered Ipomea—Color pale brown to weak yellowish orange; odor distinct, somewhat aromatic; taste sweet, becoming somewhat acrid; starch grains up to 35 microns in diameter, mostly simple, also 2- to 4-compound, and usually with a central cleft; calcium oxalate crystals numerous, mostly in rosette aggregates, occasionally in rhombohedra, from 10 to 45 microns in length; fragments of

Database: Medline <1966 to present>

Set	Search	Results
1	exp hydrocarbons, iodinated/	2722
2	iodoform.tw.	103
3	exp safety/	8472
4	efficacy.tw.	108250
5	2 and 3	0
6	2 and 4	6
7	from 6 keep 3-5	3

<1>
Unique Identifier
96081121
Authors
Corbridge RJ. Djazaeri B. Hellier WP. Hadley J.
Title
A prospective randomized controlled trial comparing the use of merocel nasal tampons and BIPP in the control of acute epistaxis.
Source
Clinical Otolaryngology. 20(4):305-7, 1995 Aug.
Abstract
A prospective study was undertaken to compare the efficacy of Merocel nasal tampons to BIPP (Bismuth Subnitrate and Iodoform Paste) impregnated ribbon gauze in the control of acute epistaxis requiring hospital admission. A total of 50 patients presenting with severe epistaxis was treated with either merocel nasal tampons, or BIPP. The groups did not differ significantly in terms of age, sex distribution, aetiology or severity of the bleed. There was no significant difference in efficacy or patient tolerance of either treatment. It was concluded that Merocel nasal tampons should be considered effective in the first line treatment of severe epistaxis uncontrolled by simple measures. Their ease of insertion makes them suitable for use in the accident and emergency department or in general practice.

<2>
Unique Identifier
94203886
Authors
Holan G. Fuks AB.

Title
A comparison of pulpectomies using ZOE and KRI paste in primary molars: a retrospective study.
Source
Pediatric Dentistry. 15(6):403-7, 1993 Nov-Dec.
Abstract
Maintaining a successfully root-treated primary molar has the advantage of preserving the natural tooth--the best possible space maintainer. The purpose of this study was to compare the success of endodontic treatment of nonvital primary molars using ZOE with that of KRI paste. Of 78 necrotic primary molars, 34 were filled with ZOE and 44 with an iodoform-containing paste (KRI). The canals were prepared with files, rinsed with saline and filled with one of the resorbable pastes, using a spiral Lentulo on a low-speed handpiece. A radiograph was exposed immediately postoperatively to observe whether the root filling was flush, underfilled, or overfilled. The effect of length of fill on the treatment outcome also was evaluated. Teeth were examined periodically clinically and radiographically to assess success of the treatment. Follow-up interval varied from 12 to more than 48 months. Overall success rate for KRI paste was 84% versus 65% for ZOE, which was statistically significant ($P < 0.05$). Overfilling with ZOE led to a failure rate of 59% as opposed to 21% for KRI ($P < 0.02$). Conversely, underfilling led to similar results, with a failure rate of 17% for ZOE and 14% for KRI. These results support the clinical efficacy of root filling with KRI paste as a treatment option for nonvital primary molars.

<3>
Unique Identifier
94087045
Authors
von Schoenberg M. Robinson P. Ryan R.
Title
Nasal packing after routine nasal surgery--is it justified?.
Source
Journal of Laryngology & Otology. 107(10):902-5, 1993 Oct.
Abstract
Ninety-five patients undergoing routine nasal surgery were enrolled into a randomized, prospective trial to investigate the efficacy and morbidity of nasal packing. The patients were randomized to receive a bismuth iodoform paraffin paste (BIPP) pack, a Telfa pack or no pack. Patients for septal surgery were randomized between the

BIPP and Telfa groups only. They were independently randomized to receive or not receive, a silastic nasal splint for the first post-operative week. Post-operative pain levels were analysed using a visual analogue scale. Mean pain scores were increased 50 per cent by the use of nasal packs and pack removal, particularly BIPP which, was a most painful event ($p < 0.001$). Reactionary haemorrhage occurred in only two patients (2.1 per cent), both of whom had packs in situ. Vestibulitis was unique to the patients with a silastic splint, who were packed with BIPP, occurring in 21 per cent of them. Similarly septal perforation was unique to this group. There was no significant difference in the incidence of adhesions between the groups which received packs and those who did not. Routine nasal packing, especially with BIPP, would seen difficult to justify in view of the increased pain levels and increased complications which occur without any demonstrable benefit in the majority of patients. Therefore packing should be reserved for cases where there is concern about persistent haemorrhage. In these cases Telfa would be preferable to BIPP.

A. INGREDIENT NAME:

METRONIDAZOLE BENZOATE

B. Chemical Name:

5-nitro-1*H*-imidazol-1-ylethyl benzoate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.54% calculated as dried basis

E. Information about how the ingredient is supplied:

White or slightly yellowish, crystalline powder

F. Information about recognition of the substance in foreign pharmacopeias:

The Indian Pharmacopeia Volume I (A-P) 1985

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Stolze, K. Elimination of Elyzol 25% Dentagel matrix from periodontal pockets. *J Clin Periodontol,* 1995; 22(3): 185-187.

H. Information about dosage forms used:

Suspension

I. Information about strength:

400mg- 3 times daily, for 5 - 10 days

J. Information about route of administration:

Topically

K. Stability data:

Melts at about 99-102°
Keep container tightly closed

L. Formulations:

M. Miscellaneous Information:

Milan, 11th December 1997

2 x 25-kg drums

30-1559
#55197

Manuf. date : July 1997
Expiry date : July 2002

ANALYSIS CERTIFICATE No. 3243

Your Ord. No. of the 10th Dec. 1997 Our Ref. No. 2925

MATERIAL METRONIDAZOLE BENZOATE B.P. micronized	Quantity	Batch
	KG. 50.-	0712

Empirical formula

Molecular weight

Aspect micronized powder

Color slig. yellowish

Odor

Taste

Melting point 99 - 102°C

Boiling range

Solubility practically insoluble in water; freely soluble in Dichloromethone; soluble in Acetone.

pH (acidity) 0.09 ML

Specific rotation

Light absorption

Loss on drying 0.1483%

Residue on ignition 0.0398%

Chloride

Sulfate

Heavy metals Less than 20 ppm

Identification : A) Melting 99 - 102°C
B) complies
C) -
D) Related substances pa
E) te

Titer (Assay) 99.54% calculated as dried basis

Other requirements, notes Results of test or analysis as per B.P.

The Analyst 12/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: METRONIDAZOLE BENZOATE POWDER

MANUFACTURE LOT NO.: 0712

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE OR SLIGHTLY CREAM TO YELLOWISH, CRYSTALLINE POWDER OR FLAKES.

2) SOLUBILITY.:
VERY SOLUBLE IN CHLOROFORM, ALCOHOL; SOLUBLE IN ETHER, INSOLUBLE IN WATER.

3) MELTING POINT.:
MELTS AT ABOUT 99-102 degree. K

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES BY IR SPECTRUM AS PER COMPANY SPECS.
B) A SOLUTION PH IS 5.8.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

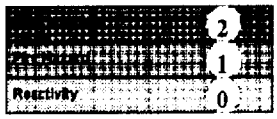
PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

SPECTRUM®

GARDENA, CA
NEW BRUNSWICK, NJ

Material Safety Data Sheet

NFPA	HMIS	Personal Protective Equipment
		
		See Section 15.

Section 1. Chemical Product and Company Identification

Common Name/ Trade Name	**Metronidazole benzoate**
Manufacturer	SPECTRUM CHEMICAL MFG. CORP. 14422 SOUTH SAN PEDRO STREET GARDENA, CALIFORNIA 90248
Commercial Name(s)	Not available.
Synonym	2-Methyl-5-nitroimidazole-1-ethanol benzoate
Chemical Name	Not available.
Chemical Family	Not available.
Chemical Formula	C13H13N3O4
Supplier	SPECTRUM QUALITY PRODUCTS, INC. 14422 SOUTH SAN PEDRO STREET GARDENA, CA 90248

Code	M4064
CAS#	13182-89-3
RTECS	Not available.
TSCA	Not on the TSCA list.
CI#	Not available.

IN CASE OF EMERGENCY
CHEMTREC (24hr) 800-424-9300
Emergency phone: (310)516-8000

Section 2.Composition and Information on Ingredients

		Exposure Limits			
Name	**CAS #**	**TWA (mg/m³)**	**STEL (mg/m³)**	**CEIL (mg/m³)**	**% by Weight**
Metronidazole benzoate	13182-89-3				100

Toxicological Data on Ingredients

Metronidazole benzoate
LD50: Not available.
LC50: Not available.

Section 3. Hazards Identification

Potential Acute Health Effects

Slightly dangerous to dangerous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation. This product may irritate eyes and skin upon contact.

Potential Chronic Health Effects

CARCINOGENIC EFFECTS: Not available. **MUTAGENIC EFFECTS**: Not available. **TERATOGENIC EFFECTS**: Not available. Toxicity of the product to the reproductive system: Not available. There is no known effect from chronic exposure to this product. Repeated or prolonged exposure is not known to aggravate medical condition.

WARNING: This product contains a chemical known to the State of California to cause cancer.
Chemical ingredient(s) requiring this warning:

NONE

WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.
Chemical ingredient(s) requiring this warning:

NONE

Continued on Next Page

Section 4. First Aid Measures

Eye Contact	Check for and remove any contact lenses. DO NOT use an eye ointment. Seek medical attention.
Skin Contact	If the chemical got onto the clothed portion of the body, remove the contaminated clothes as quickly as possible, protecting your own hands and body. Place the victim under a deluge shower. If the chemical touches the victim's exposed skin, such as the hands: Gently and thoroughly wash the contaminated skin with running water and non-abrasive soap. Be particularly careful to clean folds, crevices, creases and groin. Cover the irritated skin with an emollient. If irritation persists, seek medical attention. Wash contaminated clothing before reusing.
Serious Skin Contact	Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek medical attention.
Inhalation	Allow the victim to rest in a well ventilated area. Seek immediate medical attention.
Serious Inhalation	No additional information.
Ingestion	Remove dentures if any. Have conscious person drink several glasses of water or milk. INDUCE VOMITING by sticking finger in throat. Lower the head so that the vomit will not reenter the mouth and throat. NEVER give an unconscious person anything to ingest. Seek medical attention.
Serious Ingestion	No additional information.

Section 5. Fire and Explosion Data

Flammability of the Product	Combustible.
Auto-Ignition Temperature	Not available
Flash Points	Not available.
Flammable Limits	Not available.
Products of Combustion	These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...).
Fire Hazards in Presence of Various Substances	No specific information is available in our database regarding the flammability of this product in presence of various materials.
Explosion Hazards in Presence of Various Substances	Risks of explosion of the product in presence of mechanical impact: Not available. Risks of explosion of the product in presence of static discharge: Not available. No specific information is available in our database regarding the product's risks of explosion in the presence of various materials.
Fire Fighting Media and Instructions	SMALL FIRE: Use DRY chemicals, CO2, water spray or foam. LARGE FIRE: Use water spray, fog or foam. DO NOT use water jet.
Special Remarks on Fire Hazards	No additional remark.
Special Remarks on Explosion Hazards	No additional remark.

Section 6. Accidental Release Measures

Small Spill	Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.
Large Spill	Our database contains no additional information in case of a spill and/or a leak of the product. Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Continued on Next Page

Section 7. Handling and Storage

Precautions	Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. DO NOT breathe dust. In case of insufficient ventilation, wear suitable respiratory equipment. If you feel unwell, seek medical attention and show the label when possible. Avoid contact with skin and eyes.
Storage	Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Combustible materials should be stored away from extreme heat and away from strong oxidizing agents.

Section 8. Exposure Controls/Personal Protection

Engineering Controls	Use process enclosures, local exhaust ventilation, or other engeneering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.
Personal Protection	Splash goggles. Lab coat. Dust respirator. Be sure to use a MSHA/NIOSH approved respirator or equivalent. Gloves (impervious).
Personal Protection in Case of a Large Spill	Splash goggles. Full suit. Dust respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.
Exposure Limits	Not available.

Section 9. Physical and Chemical Properties

Physical state and appearance	Solid.
Molecular Weight	275.3
pH (1% soln/water)	Not available.
Boiling Point	Not available.
Melting Point	Not available.
Critical Temperature	Not available.
ecific Gravity	Not available.
Vapor Pressure	Not available.
Vapor Density	Not available.
Volatility	Not available.
Odor Threshold	Not available.
Water/Oil Dist. Coeff.	Not available.
Ionicity (in Water)	Not available.
Dispersion Properties	Not available.
Solubility	Not available.

Odor	Not available.
Taste	Not available.
Color	Not available.

Section 10. Stability and Reactivity Data

Stability	The product is stable.
Instability Temperature	Not available.
Conditions of Instability	No additional remark.
Incompatibility with various substances	No specific information is available in our database regarding the reactivity of this material in presence of various other materials.
Corrosivity	Non-corrosive in presence of glass.
Special Remarks on Reactivity	No additional remark.
Special Remarks on Corrosivity	No additional remark.
olymerization	No.

Continued on Next Page

Section 11. Toxicological Information

Routes of Entry	Ingestion. Inhalation.
Toxicity to Animals	LD50: Not available LC50: Not available
Chronic Effects on Humans	Toxicity of the product to the reproductive system: Not available
Other Toxic Effects on Humans	Slightly dangerous to dangerous in case of skin contact (irritant), of eye contact (irritant), of ingestion, of inhalation.
Special Remarks on Toxicity to Animals	No additional remark.
Special Remarks on Chronic Effects on Humans	No additional remark.
Special Remarks on other Toxic Effects on Humans	No additional remark.

Section 12. Ecological Information

Ecotoxicity	Not available.
BOD5 and COD	Not available.
Products of Biodegradation	These products are carbon oxides (CO, CO2), nitrogen oxides (NO, NO2...).
Toxicity of the Products of Biodegradation	The products of degradation are more toxic.
Special Remarks on the Products of Biodegradation	No additional remark.

Section 13. Disposal Considerations

Waste Disposal	Recycle to process, if possible. Consult your local or regional authorities.

Section 14. Transport Information

DOT Classification	Not a DOT controlled material (United States).
Identification	Not applicable (PIN and PG).
Special Provisions for Transport	Not applicable.
DOT (Pictograms)	

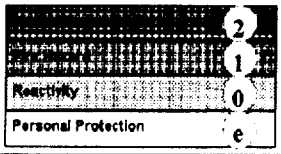
Section 15. Other Regulatory Information and Pictograms

Federal and State Regulations	Not available.
California Proposition 65 Warnings	**WARNING: This product contains a chemical known to the State of California to cause cancer.** **Chemical ingredient(s) requiring this warning:** **NONE** **WARNING: This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.** **Chemical ingredient(s) requiring this warning:** **NONE**
Other Regulations	OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

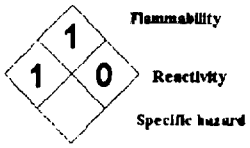
Continued on Next Page

Other Classifications	**WHMIS (Canada)**	Not controlled under WHMIS (Canada).
	DSCL (EEC)	Not controlled under DSCL (Europe).

HMIS (U.S.A.)



National Fire Protection Association (U.S.A.)



WHMIS (Canada) (Pictograms)

DSCL (Europe) (Pictograms)

TDG (Canada) (Pictograms)

ADR (Europe) (Pictograms)

Protective Equipment

Gloves (impervious).

Lab coat.

Dust respirator. Be sure to use a MSHA/NIOSH approved respirator or equivalent.

Splash goggles.

Section 16. Other Information

Catalog Number(s)	**M1183**
References	Not available.
Other Special Considerations	No additional remark.

Validated by E. Brull on 9/26/97.	**Verified by E. Brull.** **Printed 9/30/97.**

mergency phone: (310)516-8000

Notice to Reader

Continued on Next Page

Storage Store in a well-closed container, protected from light.

Preparation

Methylprednisolone Acetate Injection

Action and use Corticosteroid.

1/95

Metoprolol Tartrate

Identification Test A. Line 4. For '18°' read '−18°'. Line 6. After 'residue' insert ', Appendix II A'.

12/93

Heavy metals Line 2. For '1 ml' read '10 ml'.

7/94

Add the following statement.

Preparations

Metoprolol Injection

Metoprolol Tartrate Tablets

Metronidazole

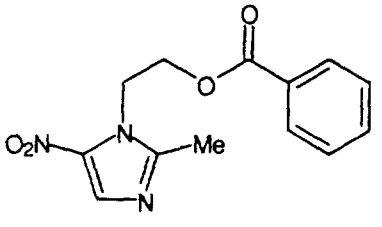
Add a five-pointed star (☆) to the title.

7/94

Preparations Add the following:

Metronidazole Intravenous Infusion

Metronidazole Benzoate ☆



$C_{13}H_{13}N_3O_4$ 275.3 *13182-89-3*

Definition Metronidazole Benzoate contains not less than 98.5% and not more than 101.0% of 2-(2-methyl-5-nitro-1*H*-imidazol-1-ylethyl benzoate, $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Characteristics White or slightly yellowish, crystalline powder or flakes; practically insoluble in *water*; freely soluble in *dichloromethane*; soluble in *acetone*; slightly soluble in *ethanol (96%)*; very slightly soluble in *ether*.

Identification *Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.*

A. *Melting point*, 99° to 102°, Appendix V A, Method I.

B. Dissolve 0.1 g in 1M *hydrochloric acid* and dilute to 100 ml with the same acid. Dilute 1 ml of the solution to 100 ml with 1M *hydrochloric acid*. Examined between 220 nm and 350 nm, Appendix II B, the solution shows two absorption maxima, at 232 nm and 275 nm. The *specific absorbance* at the maximum at 232 nm is 525 to 575.

C. Examine by *infrared absorption spectrophotometry*, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with *metronidazole benzoate EPCRS*.

D. Examine the chromatograms obtained in the test for Related substances under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of *zinc powder*, 1 ml of *water* and 0.3 ml of *hydrochloric acid*. Heat on a water bath for 5 minutes and cool. The solution yields the reaction characteristic of *primary aromatic amines*, Appendix VI.

Appearance of solution Dissolve 1 g in *dimethylformamide* and dilute to 10 ml with the same solvent. The solution is not more opalescent than *reference suspension II*, Appendix IV A, and not more intensely coloured than *reference solution* GY_3, Appendix IV B, Method II.

Acidity Dissolve 2 g in a mixture of 20 ml of *dimethylformamide* and 20 ml of *water*, previously neutralised with 0.02M *hydrochloric acid VS* or 0.02M *sodium hydroxide VS* using 0.2 ml of *methyl red solution*. Not more than 0.25 ml of 0.02M *sodium hydroxide VS* is required to change the colour of the indicator.

Related substances Examine by *thin-layer chromatography*, Appendix III A, using *silica gel* HF_{254} as the coating substance. Heat the plate at 110° for 1 hour and allow to cool before use.

Solution (1) Dissolve 0.20 g of the substance being examined in *acetone* and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with *acetone*.

Solution (3) Dissolve 20 mg of *metronidazole benzoate EPCRS* in *acetone* and dilute to 10 ml with the same solvent.

Solution (4) Dilute 5 ml of solution (2) to 100 ml with *acetone*.

Solution (5) Dilute 2 ml of solution (2) to 100 ml with *acetone*.

Solution (6) Dissolve 10 mg of *metronidazole EPCRS* in *acetone* and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of *2-methyl-5-nitroimidazole* in *acetone* and dilute to 100 ml with the same solvent.

Solution (8) Dissolve 10 mg of *metronidazole EPCRS* and 10 mg of *2-methyl-5-nitroimidazole* in *acetone* and dilute to 50 ml with the same solvent.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using *ethyl acetate*. Allow the plate to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to metronidazole or 2-methyl-5-nitroimidazole is not more intense than the corresponding spot in the chromatograms obtained with solutions (6) and (7) respectively (0.5%). Any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram

Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume – I
(A – P)

Third Edition

PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.45 g and dissolve in 10 ml of *glacial acetic acid*, add a few drops of *1-naphtholbenzein solution* and titrate with *0.1N perchloric acid* until a pale-green colour is produced. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed light-resistant containers.

Metronidazole Tablets

Category : Anti-amoebic; antitrichomonal; antigiardial.

Dose : Metronidazole. For trichomoniasis, 200 mg three times daily, for 7 days.

For amoebiasis, 400 mg three times daily, for 8 to 10 days.

For giardiasis, 2 g daily for three successive days for adults, 1 g daily for children and 400 mg daily for infants.

Usual strengths : 200 mg; 400 mg.

Standards : Metronidazole Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Metronidazole, $C_6H_9N_3O_3$. The tablets may be coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to about 0.2 g of Metronidazole with 4 ml of *N sulphuric acid* and filter. To the filtrate add 10 ml of *picric acid solution* and alow to stand for one hour, the precipitate after washing with cold *water* under suction and drying at 105° melts at about 150°, Appendix 5.11.

(B) Comply with **Identification** test (B) described under Metronidazole, using a quantity of the powdered tablets equivalent to 10 mg of Metronidazole.

2-Methyl-5-nitroimidazole : Comply with the test described under Metronidazole, using as solution (1), a solution prepared in the following manner: Shake a quantity of the powdered tablets equivalent to 0.2 g of Metronidazole with 5 ml of mixture of equal volumes of *chloroform* and *methyl alcohol* for five minutes and filter. The chromatogram obtained with solution (1) may also show spots due to excipients.

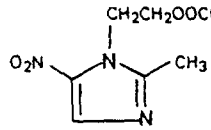
Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.2 g of Metronidazole, transfer to a sintered-glass crucible and extract with six quantities, each of 10 ml, of hot *acetone*. Cool, add to the combined extracts 50 ml of *acetic anhydride*, 0.1 ml of a 1 per cent w/v solution of *brilliant green* in *glacial acetic acid* and titrate with *0.1N perchloric acid* to a yellowish-green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed, light-resistant containers.

Metronidazole Benzoate

Benzoyl Metronidazole



$C_{13}H_{13}N_3O_4$ Mol. Wt. 275.27

Category : Anti-amoebic.

Dose : For amoebic dysentry, the equivalent of 400 mg of metronidazole three times, daily, for 5 to 10 days.

NOTE – 200 mg of Metronidazole Benzoate is approximately equivalent to 125 mg of metronidazole.

Description : White or cream-coloured crystalline powder, odourless; almost tasteless.

Solubility : Sparingly soluble in *water*; soluble in *chloroform*, in *acetone*, and in *alcohol (90 per cent)*.

Standards : Metronidazole Benzoate is 2-(2-methyl-5-nitro-imidazol-1-yl) ethyl benzoate. It contains not less than 98.0 per cent of $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Identification : (A) The light absorption, in the range 230 to 530 nm of a 1-cm layer of a 0.001 per cent w/v solution in *ethyl alcohol* exhibits a maximum only at 309 nm; *extinction* at 309 nm, about 0.3, Appendix 5.15 A.

(B) It gives the reactions of *benzoates*, Appendix 3.1.

Melting range : Between 100° and 102°, Appendix 5.11.

pH : Between 5.0 and 7.0, determined in a 2.0 per cent w/v suspension, Appendix 5.10.

Free benzoic acid : Not more than 0.2 per cent, determined by the following method: Dissolve 0.50 g in 25 ml of *alcohol* and titrate with *0.1N sodium hydroxide*, using *phenol red solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of

0.1N sodium hydroxide is equivalent to 0.01221 g of $C_7H_6O_2$.

Related substances : Carry out the method for *thin-layer chromatography*, Appendix 5.4.3, using *silica gel HF 254* as the coating substance and a mixture of 8 volumes of *chloroform* and 2 volumes of *acetone* as the mobile phase. Apply separately to the plate 10 µl of each of three solutions in a mixture of equal volumes of *methyl alcohol* and *chloroform* containing (1) 6.0 per cent w/v of the substance being examined; (2) 0.02 per cent w/v of *2-methyl-5-nitroimidazole R.S.* and; (3) 0.02 per cent w/v of *metronidazole R.S.* After removal of the plate, allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spots in the chromatogram obtained with solutions (2) and (3) are more intense than any corresponding spots in the chromatogram obtained with solution (1).

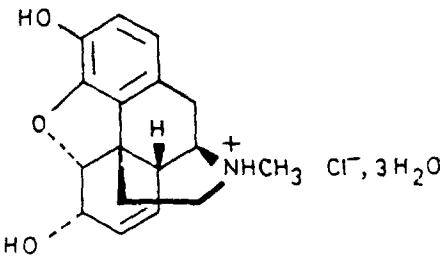
Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying "in vacuo at 60°," Appendix 5.8.

Assay : Weigh accurately about 0.5 g and dissolve in 50 ml of *acetone*. Add 10 ml of *acetic anhydride* and titrate with *0.1N perchloric acid* using *brilliant green solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.02753 g of $C_{13}H_{13}N_3O_4$.

Storage : Store in well-closed, light-resistant containers.

Morphine Hydrochloride



$C_{17}H_{19}NO_3, HCl, 3H_2O$ Mol. Wt. 375.85

Category : Narcotic, analgesic.

Dose : 10 to 20 mg.

Description : Colourless, glistening needles or white crystalline powder; odourless; taste, bitter.

Solubility : Soluble in *water*; sparingly soluble in *alcohol*; practically insoluble in *solvent ether* and in *chloroform*; soluble in *glycerin*.

Standards : Morphine Hydrochloride is the trihydrate of the hydrochloride of 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol, which may be obtained from opium. It contains not less than 98.0 per cent and not more than the equivalent of 100.5 per cent of $C_{17}H_{19}NO_3$, HCl, calculated with reference to the dried substance.

Identification : (A) Sprinkle a small quantity in powder form on the surface of a drop of *nitric acid*; an orange-red colour is produced.

(B) To a 2 per cent w/v solution add *potassium ferricyanide solution* containing 1 drop per ml of *ferric chloride test-solution*; an immediate bluish-green colour is produced (distinction from codeine).

(C) Add 5 ml of *sulphuric acid* to 5 mg in a test-tube, and add 1 drop of *ferric chloride test-solution*, and heat in boiling water for two minutes; a deep blue colour is produced. Add a drop of *nitric acid*; the colour changes to dark red-brown (codeine and ethylmorphine give the same colour reactions, but dihydromorphine and papaverine do not produce this colour change).

(D) Add to about 1 mg of the powdered substance in a porcelain dish 0.5 ml of *sulphuric acid* containing 1 drop of *formaldehyde solution*. A purple colour is formed which turns to violet.

(E) Dissolve about 5 mg in 5 ml of *water*, and add 1 ml of *hydrogen peroxide solution*, 1 ml of *dilute ammonia solution* and 1 drop of a 4 per cent w/v solution of *copper sulphate*. A transient red colour develops.

(F) A solution (1 in 20) gives the reactions of *chlorides*, Appendix 3.1.

Acidity or Alkalinity : Dissolve 0.2 g in 10 ml of freshly boiled and cooled *water* add 1 drop of *methyl red solution*. Not more than either 0.2 ml of *0.02N sodium hydroxide* or of *0.02N hydrochloric acid* is required to change the colour of the solution.

Specific optical rotation : Between −112° and −115°, calculated with reference to the dried substance and determined in a 2 per cent w/v solution, Appendix 5.12.

Ammonium salts : Heat 0.2 g with *sodium hydroxide solution* on a water-bath for one minute; no odour of ammonia is perceptible.

Other alkaloids : Not more than 1.5 per cent, calculated with reference to the dried substance, determined by the following method: Transfer 0.5 g to a separator, add 15 ml of *water*, 5 ml of *N sodium hydroxide*, and 10 ml of *chloroform*, shake, allow to separate, and transfer the chloroform solution to another separator. Repeat the extraction with two further quantities, each of 10 ml, of *chloroform*. Wash the mixed chloroform solutions with 10 ml of *0.1N sodium hydroxide* and then with two successive quantities, each of 5 ml, of *water*, evaporate to dryness on a water-bath, and dry the residue to constant weight at 105°.

National Library of Medicine: IGM Full Record Screen

TITLE: Elimination of Elyzol 25% Dentalgel matrix from periodontal pockets.

AUTHOR: Stoltze K

AUTHOR AFFILIATION: Department of Periodontology, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark.

SOURCE: J Clin Periodontol 1995 Mar;22(3):185-7

NLM CIT. ID: 95310528

ABSTRACT: Elyzo 25% Dentalgel (EDG) which is developed for use in the treatment of periodontitis is a suspension of metronidazole benzoate (40%) in a mixture of glyceryl mono-oleate (GMO) and triglyceride (sesame oil). Metronidazole can be detected in the periodontal pockets 24-36 h after application. The aim of the present study was to estimate the period of time that the gel matrix persists on periodontal pockets after 1 application of EDG. 12 patients were included in the study. From each patient, 1 sample was taken before and immediately after, and 1, 2, 3, 4, 5, 6, 8, 12 and 24 h after application. Subgingival scaling followed by absorption of gingival crevicular fluid with filter paper was used for sampling. The sampling unit was 1 tooth. Each sample was assayed for the amount of GMO and oleic acid (a degradation product of GMO) by means of high-performance liquid chromatography (HPLC) with UV detection. To allow determination of the GMO dose applied into the pockets and to estimate the recovery rate of the sampling method, 1 tooth in each patient was selected for sampling as soon as the gel had set, i.e., about 10 min after application. Only in 1 patient was a detectable amount of GMO within the pocket revealed 24 h after application. This amount was approximately 0.5% of the mean GMO dose applied around 1 tooth. GMO was found no longer than 12 h in the remaining patients.

MAIN MESH SUBJECTS: Glycerides/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS
Metronidazole/*ANALOGS & DERIVATIVES/ADMINISTRATION & DOSAGE/ ANALYSIS/*PHARMACOKINETICS
Periodontal Pocket/*METABOLISM
Sesame Oil/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS

A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:

Argentum Crede, Collargol (9CI), Colloidal Silver, Stillargol, Vitargénol, Aust.: Coldargan, Fr.: Pastaba, Ger.: Coldargan, Ital.: Arscolloid, Bio-Arscolloid, Corti-Ascolloid, Rikosilver, Rinatipiol, Rinovit Nube.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay: (after ignition)	19.0-23.0%	19.74%

E. Information about how the ingredient is supplied:

Brown, Dark-Brown,or almost black, odorless, lustrous scales or granules, somewhat hygroscopic, and is affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Cz., Fr., Hung., It., and Jpn.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Isenberg, S., Apt, L., and Yoshimuri. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Archives of Opthalmology,* 1983; 101(5): 764-765.

Apt, L. and Isenberg, S. Chemical preparation of skin and eye in ophthalmic surgery: an international survey. *Opthalmic Surgery,* 1982; 13(12): 1026-1029.

H. Information about dosage forms used:

Liquid

I. Information about strength:

1-20%

J. Information about route of administration:

Nasal
Opthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

30-1263
51149

CERTIFICATE OF ANALYSIS

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT # :B61695G18

GRADE:NFXIII
CODE:D5785

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	Black granules	Conforms
2.	Identification	To pass test	Passes test
3.	Solubility	To pass test	Passes test
4.	Assay (after ignition) D	19.0 - 23.0%	19.74%
5.	Ionic silver	No turbidity	Conforms
6.	Distinction from strong silver protein	To pass test	Passes test

ATTENTION: TONY HATCHETT

Date :06/23/97

10762

Prepared by : A. HAZARI

Approved by: 6/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: SILVER PROTEIN MILD NF A

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1)DESCRIPTION.:
E { BROWN,DARK-BROWN,OR ALMOST BLACK,ODORLESS,LUSTROUS SCALES OR GRANULES; SOMEWHAT HYGROSCOPIC,AND IS AFFECTED BY LIGHT.

2)SOLUBILITY.:
FREELY SOLUBLE IN WATER. ALMOST INSOLUBLE IN ALCOHOL,CHLOROFORM AND IN ETHER.

3)MELTING POINT.:

4)SPECIFIC GRAVITY .:

5)IDENTIFICATION.:
A)COMPLIES (B) AS PER NF 10th EDITION 1955.
B)COMPLIES (C) AS PER NF 10th EDITION 1955.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

---------- IDENTIFICATION ----------

PRODUCT #: 29824-7 NAME: SILVER PROTEIN, MILD

CAS #: 9015-51-4

SYNONYMS

ARGENTUM CREDE * COLLARGOL (9CI) * COLLOIDAL SILVER *

---------- TOXICITY HAZARDS ----------

RTECS NO: VW3675000

SILVER, COLLOIDAL

TOXICITY DATA

ORL-MUS LD50:100 MG/KG JPPMAB 2,20,50

REVIEWS, STANDARDS, AND REGULATIONS

ACGIH TLV-TWA 0.01 MG(AG)/M3 85INA8 5,529,86

MSHA STANDARD-AIR:TWA 0.01 MG(AG)/M3 DTLVS* 3,231,71

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE EYE IRRITATION.

MAY CAUSE SKIN IRRITATION.

TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS

AMOUNTS OF WATER FOR AT LEAST 15 MINUTES WHILE REMOVING CONTAMINATED

CLOTHING AND SHOES.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

WASH CONTAMINATED CLOTHING BEFORE REUSE.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

DARK-BROWN OR BLACK FLAKES

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.
---------- REACTIVITY DATA ----------
INCOMPATIBILITIES
STRONG OXIDIZING AGENTS
PROTECT FROM LIGHT.
ACIDS
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
EVACUATE AREA.
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT
GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
SAFETY SHOWER AND EYE BATH.
USE ONLY IN A CHEMICAL FUME HOOD.
DO NOT BREATHE DUST.
AVOID CONTACT WITH EYES, SKIN AND CLOTHING.
AVOID PROLONGED OR REPEATED EXPOSURE.
WASH THOROUGHLY AFTER HANDLING.
TOXIC.
KEEP TIGHTLY CLOSED.
LIGHT SENSITIVE
STORE IN A COOL DRY PLACE.
TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE

POSSIBLE).
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

REGULATORY INFORMATION
20.0% SILVER COMPOUND
THIS PRODUCT IS SUBJECT TO SARA SECTION 313 REPORTING REQUIREMENTS.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

Sesame Oil (7368-w)

Aceite de Ajonjolí; Benne Oil; Gingelly Oil; Oleum Sesami; Teel Oil.

Pharmacopoeias. In *Aust., Belg., Br., Chin., Eur., Fr., Ger., It., Jpn, Neth., Port.,* and *Swiss.* Also in *USNF.*

The standards of *Ph. Eur.* apply to those countries that are party to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

The fixed oil obtained from the ripe seeds of *Sesamum indicum* (Pedaliaceae) by expression or extraction and subsequent refining. It is a clear pale yellow oil, almost odourless and with a bland taste with a fatty-acid content consisting mainly of linoleic and oleic acids. It solidifies to a buttery mass at about −4°.

Slightly **soluble** to practically insoluble in alcohol; miscible with carbon disulphide, chloroform, ether, and petroleum spirit. **Store** at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been observed.

Shellac (285-x)

904; Gomme Laque; Lacca; Lacca in Tabulis; Schellack.

Pharmacopoeias. In *Fr.* and *Ger.* Also in *USNF.*

Jpn includes Purified Shellac and White Shellac (Bleached).

Shellac is obtained by purification of the resinous secretion of the insect *Laccifer lacca* Kerr (Coccidae). The USNF describes 4 grades: Orange Shellac is produced by filtration in the molten state or by a hot solvent process, or both; removal of the wax produces Dewaxed Orange Shellac; Regular Bleached (White) Shellac is prepared by dissolving the secretion in aqueous sodium carbonate, bleaching with hypochlorite, and precipitating with sulphuric acid; removal of the wax by filtration during the process produces Refined Bleached Shellac.

Practically **insoluble** in water; very slowly soluble in alcohol 85% to 95% (w/w); soluble in ether, 13% to 15%, and in aqueous solutions of ethanolamines, alkalis, and borax. **Store** preferably at a temperature not exceeding 8°.

Shellac is used as an enteric coating for pills and tablets, but [illegible]tegration time has been reported to increase markedly on [illegible]ge.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USNF 18: Pharmaceutical Glaze.

Siam Benzoin (273-c)

Benjoin du Laos; Benzoe Tonkinensis.

Pharmacopoeias. In *Aust., Chin., Fr., It.,* and *Swiss.* Also in many pharmacopoeias under the title benzoin and should not be confused with Sumatra Benzoin. *Hung., Jpn,* and *US* allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

A balsamic resin from *Styrax tonkinensis* (Styracaceae) and containing not more than 10% of alcohol (90%)-insoluble matter.

Yellowish-brown to rusty brown compressed pebble-like tears with an agreeable, balsamic, vanilla-like odour. The tears are separate or very slightly agglutinated, milky white on fracture, [illegible] and brittle at ordinary temperatures, but softe[illegible]

Sia[illegible]en used similarly to Sumatra benzoin (p.17[illegible]een used as a preservative and was formerly [illegible]ration of benzoinated lard.

Prepar[illegible]

Names of pr[illegible]isted below; details are given in Part 3.

Official [illegible]

USP 23: Com[illegible] Tincture; Podophyllum Resin Topical Solution.

Proprietary Prep[illegible]

Multi-ingredient pre[illegible]s. *Canad.:* Benzoinspray†; Cold Sore Lotion†; *Ital.:* Ond[illegible]ain: Vahos Balsamicos†.

Silver (5316-v)

E174.

[illegible] = 107.8682.

[illegible] — 7440-22-4.

[illegible]armacopoeias. In *Swiss.*

A pure white, malleable and duc[illegible]l.

Silver possesses antibacterial prop[illegible]nd is used topically either as the metal or as silver salt[illegible]t absorbed to any great extent and the main problem [illegible]ed with the metal is argyria, a general grey discoloration. Silver is used as a colouring agent for some types of confectionery. It is also used as Argentum Metallicum in homeopathy.

Numerous salts or compounds of silver have been employed for various therapeutic purposes, including silver acetate (p.1751), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (p.1751), silver-nylon polymers, silver protein (p.1751), and silver sulphadiazine (p.273).

A report of reversible neuropathy associated with the absorption of silver from an arthroplasty cement.[1]

1. Vik H, *et al.* Neuropathy caused by silver absorption from arthroplasty cement. *Lancet* 1985; **i:** 872.

Coating catheters with silver has been reported to reduce the incidence of catheter-associated bacteriuria,[1,2] but other studies have reported increased infection.[3]

1. Lundeberg T. Prevention of catheter-associated urinary-tract infections by use of silver-impregnated catheters. *Lancet* 1986; **ii:** 1031.
2. Johnson JR, *et al.* Prevention of catheter-associated urinary tract infections with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. *J Infect Dis* 1990; **162:** 1145–50.
3. Riley DK, *et al.* A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995; **98:** 349–56.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Austral.: Micropur; *Canad.:* Tabanil; *Ger.:* Dulcargant; Silargetten†.

Multi-ingredient preparations. *Austral.:* Sima-Varix Bandage†; Simanite†; *Fr.:* Stérilet T au Cuivre Argent†; *Ger.:* Adsorgan†; Grüne Salbe "Schmidt" N; *Ital.:* Actisorb Plus; Agipiù; Katoderm; Katoxyn; Nova-T; Silver-Nova T†; *Spain:* Argentocromo; *UK:* Actisorb Plus.

Silver Acetate (5319-p)

Argenti Acetas.

CH_3COOAg = 166.9.

CAS — 563-63-3.

Pharmacopoeias. In *Aust.* and *Hung.*

Silver acetate has been used similarly to silver nitrate as a disinfectant. It has also been used in antismoking preparations.

References.

1. Jensen EJ, *et al.* Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. *Hum Toxicol* 1988; **7:** 535–40.
2. Gourlay SG, McNeill JJ. Antismoking products. *Med J Aust* 1990; **153:** 699–707.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Tabmint.

Silver Nitrate (5321-h)

Argenti Nitras; Nitrato de Plata; Nitrato de Prata.

$AgNO_3$ = 169.9.

CAS — 7761-88-8.

Pharmacopoeias. In *Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Int., It., Jpn, Neth., Port., Swiss,* and *US.*

The standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

Colourless or white transparent crystals or crystalline odourless powder. On exposure to light in the presence of organic matter, silver nitrate becomes grey or greyish-black.

Soluble 1 in 0.4 of water and 1 in 30 of alcohol; its solubility is increased in boiling water or alcohol; slightly soluble in ether. A solution in water has a pH of about 5.5.

Silver nitrate is **incompatible** with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility. **Store** in airtight non-metallic containers. Protect from light.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.[1]

1. *PSGB Lab Report P/80/6* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, diarrhoea, vomiting, coma, and convulsions.

A short lived minor conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria, which though difficult to treat is considered to be mainly a cosmetic hazard, see under Silver (above).

Absorption of nitrite following reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Treatment of these adverse effects is symptomatic.

Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibiotics and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; **231:** 245.

Pharmacokinetics

Silver nitrate is not readily absorbed.

Uses and Administration

Silver nitrate possesses disinfectant properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.151) when 2 drops are instilled into each conjunctival sac of the neonate. However, as it can cause irritation, other agents are often used.

In stick form it has been used as a caustic to destroy warts and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical disinfectants and astringents in other conditions.

Silver nitrate (Argentum Nitricum; Argent. Nit.) is used in homoeopathic medicine. It is also used in cosmetics to dye eyebrows and eye lashes in a concentration of not more than 4%.

Cystitis. Comment on silver nitrate irrigation having limited value in the management of haemorrhagic cystitis after radiotherapy.[1]

1. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; **i:** 304–6.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations

Austral.: Howe's Solution†; Quitt†; *Ger.:* Mova Nitrat; Pluralane; *Spain:* Argenpal.

Multi-ingredient preparations. *Austral.:* Super Banish; *Spain:* Argentofenol; *Switz.:* Grafco; *UK:* AVOCA.

Silver Protein (5322-m)

Albumosesilber; Argentoproteinum; Argentum Proteinicum; Protargolum; Proteinato de Plata; Proteinato de Prata; Strong Protargin; Strong Protein Silver; Strong Silver Protein.

CAS — 9007-35-6 (colloidal silver).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinicum; Mild Protargin; Mild Silver Proteinate; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Prata.

Pharmacopoeias. In *Aust., Belg., Cz., Fr., Hung., It.,* and *Jpn.* Many of these pharmacopoeias include monographs on mild silver protein as well as on colloidal silver.

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver which is also a preparation of silver in combination with protein has also been used topically for its antibacterial activity.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Stillargol; Vitargénol.

Multi-ingredient preparations. *Aust.:* Coldargan; *Fr.:* Pastaba; *Ger.:* Coldargan†; *Ital.:* Arscolloid; Bio-Arscolloid; Corti-Arscolloid; Rikosilver; Rinantipiol; Rinovit Nube.

Slippery Elm (5458-t)

Elm Bark; Slippery Elm Bark; Ulmus; Ulmus Fulva.

Pharmacopoeias. In *US.*

The dried inner bark of *Ulmus fulva* (=*U. rubra*) (Ulmaceae).

Slippery elm contains much mucilage and has been used as a demulcent.

The symbol † denotes a preparation [illegible]er actively marketed

Epidermal necrolysis. Based on the treatment of 10 cases, the following was suggested as treatment for toxic epidermal necrolysis: continuous moist compresses of silver nitrate solution 0.25 to 0.5%, with generous wrapping to prevent excessive cooling; daily electrolyte estimations; and daily debridement; after about the fourth day the compresses could be replaced by dexamethasone/neomycin spray followed by inunction of wool alcohols ointment. A penicillin should be given routinely and steroids if vasculitis was present.— P. J. Koblenzer, *Archs Derm.*, 1967, *95*, 608.

Herpes simplex. Silver nitrate 1% had little effect *in vitro* or *in vivo* against herpes simplex virus type 2.— V. R. Coleman *et al.*, *Antimicrob. Ag. Chemother.*, 1973, *4*, 259. A further study.— F. Shimizu *et al.*, *ibid.*, 1976, *10*, 57.

Hydatid cysts. Intrahepatic cysts of *Echinococcus granulosus* were treated with excellent results in 20 patients by freezing the operation area then administering silver nitrate 0.5% to destroy the scolices.— I. Nazarian and F. Saidi, *Z. Tropenmed. Parasit.*, 1971, *22*, 188, per *Trop. Dis. Bull.*, 1971, *68*, 1356.

Ophthalmia neonatorum. In a study of the incidence of ophthalmia neonatorum in 220 000 births, it was found that in 92 865 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas where silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed no more effective than other agents. While a drop of 1% silver nitrate solution did no harm, there was little evidence that it did any good.— *Lancet*, 1949, *1*, 313.

Of the 49 states of the USA which had made regulations requiring routine prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. No evidence had been found to contra-indicate 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhoea had rendered continued routine prophylaxis necessary.—P.C. Barsam, *New Engl. J. Med.*, 1966, *274*, 731. Fewer local reactions occurred with penicillin than with silver nitrate eye-drops. Penicillin for neonatal prophylaxis should not be abandoned, since it did not appear to sensitise infants.—G. Nathenson (letter), *ibid.*, *275*, 280. Eye-drops containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and prophylaxis was advised only in infants whose mothers were known or suspected to be infected.— E. B. Shaw (letter), *ibid.*, 281. See also P. Kober, *Medsche Klin.*, 1967, *62*, 424.

To prevent gonorrhoeal ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration.— P. Thygeson, *J. Am. med. Ass.*, 1967, *201*, 902.

For reports on the chemical conjunctivitis associated with instillation of silver nitrate eye-drops and recommendations for reduction of the incidence, see Adverse Effects (above).

Pneumothorax. Spontaneous pneumothorax was successfully treated in 132 patients by pleurodesis induced with silver nitrate; repeated pleurodesis was necessary in only 2 patients. It was suggested that this therapy should be used for patients with only small or no blebs visible on thoracoscopy, or with only mild pre-existing lung disease.— I. Anderson and H. Nissen, *Dis. Chest*, 1968, *54*, 230, per *J. Am. med. Ass.*, 1968, *206*, 681.

Wounds. Silver nitrate solution 0.5% was more effective against Gram-positive than Gram-negative bacteria in the treatment of nonthermal war wounds. The solution did not hinder wound healing or epithelialisation of split thickness skin grafts.— J. P. Connors *et al.*, *Archs Surg., Chicago*, 1969, *98*, 119, per *J. Am. med. Ass.*, 1969, *207*, 580.

Preparations

Mitigated Silver Nitrate *(B.P.C. 1968)*. Argenti Nitras Mitigatus; Mitigated Caustic; Argenti Nitras Dilutus. Silver nitrate 1 and potassium nitrate 2, fused together and suitably moulded for application as a caustic to warts and condylomas. Protect from light.
A similar preparation is included in several pharmacopoeias.

Silver Nitrate Stain Remover *(Univ. of Iowa)*. Thiourea ($NH_2.CS.NH_2$=76.12) 8 g, citric acid monohydrate 8 g, water to 100 ml. It should be freshly prepared.

Toughened Silver Nitrate *(B.P.)*. Argenti Nitras Induratus; Toughened Caustic; Fused Silver Nitrate; Lunar Caustic; Moulded Silver Nitrate; Stylus Argenti Nitrici. Silver nitrate 95 and potassium nitrate 5, fused together and suitably moulded.
White or greyish-white cylindrical rods or cones, which become grey or greyish-black on exposure to light. Freely soluble in water; sparingly soluble in alcohol. Protect from light.
A similar preparation is included in several pharmacopoeias.

Toughened Silver Nitrate *(U.S.P.)*. Contains not less than 94.5% of $AgNO_3$, the remainder consisting of silver chloride. Store in airtight containers. Protect from light.

Creams

Silver Nitrate Cream. Silver nitrate, 0.5 or 2%, Xalifin-15 20%, water to 100%. The cream was stable with only slight discoloration when stored for 4 weeks in the dark at room temperature; at 0° to 4° there was no discoloration.—Pharm. Soc. Lab. Rep. P/68/15, 1968.

Eye-drops

Oculoguttae Argenti Nitratis pro Neonatis *(Dan. Disp.)*. Silver nitrate 670 mg, potassium nitrate 1.2 g, and Water for Injections, 98.13 g.
A similar preparation is included in *F.N.Belg.*

Silver Nitrate Eye-drops *(B.P.C. 1954)*. Gutt. Argent. Nit. Silver nitrate 0.5% w/v, potassium nitrate 1.33% w/v, in Solution for Eye-drops.
Nord. P. has 1% w/w with potassium nitrate 1% w/w in Water for Injections.

Ointments

Unguentum Argenti Nitratis Compositum. Compound Silver Nitrate Ointment. An ointment with this title is included in several pharmacopoeias. It contains silver nitrate 1% and Peru balsam 5 to 10% usually in a basis of yellow soft paraffin or yellow soft paraffin and wool fat.

Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution *(U.S.P.)*. A solution of silver nitrate 0.95 to 1.05% in an aqueous medium. pH 4.5 to 6. It may contain sodium acetate as a buffer. Store in single-dose containers. Protect from light.

Solutions

Ammoniacal Silver Nitrate Solution *(U.S.N.F. XII, 1965)*. Ammoniacal Silver Nitrate, Howe. A solution of diamminosilver nitrate was prepared from silver nitrate 704 g, water 245 ml, and strong ammonia solution to dissolve all but the last trace of precipitate (about 680 ml).It contains 28.5 to 30.5% w/w of Ag and 9 to 9.7% w/w of NH_3. Store in small glass-stoppered containers or in ampoules. Protect from light.
This solution has been employed in dental surgery to deposit silver in exposed dentine or to fill up small crevices in the teeth. After the solution had been applied to the tooth it was followed by a reducing agent such as a 10% formaldehyde solution or eugenol to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.

Solutio Argenti Nitratis cum Tetracaino *(Nord. P.)*. Silver nitrate 200 mg, amethocaine nitrate 100 mg, and water 99.7 g.

Proprietary Names

Helvedstensstifter *(Braun, Denm.)*; Lapis *(DAK, Denm.)*; Mova Nitrat Pippette *(Lindopharm, Ger.)*.

5322-m

Silver Protein *(B.P.C. 1968)*. Argentoproteinum; Strong Protein Silver; Strong Protargin; Argentum Proteinicum; Albumosesilber; Protargolum; Proteinato de Plata; Proteinato de Prata.

CAS — 9015-51-4.

Pharmacopoeias. In *Arg., Aust., Belg., Cz., Fr., Hung., Ind., Int., It., Jap., Pol., Port., Roum., Span.*, and *Turk.*

A brown odourless hygroscopic powder containing 7.5 to 8.5% of Ag.
Slowly **soluble** 1 in 2 of water; very slightly soluble in alcohol, chloroform, and ether. A solution in water is neutral to litmus. Solutions may be prepared by shaking the powder over the surface of cold water and allowing it to dissolve slowly, or by triturating the powder to a cream with water and diluting. Solutions are transparent and not coagulated by heat, nor precipitated by the addition of alkali, alkali sulphides, alkali salts, or albumin; they are relatively non-staining. Store in airtight containers. Protect from light.

Adverse Effects. As for Silver (above).

Uses. Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and are used as eye-drops in the treatment of conjunctivitis. Solutions are relatively non-irritant unless they contain more than 10% of silver protein.

Preparations

Silver Protein Eye-drops *(B.P.C. 1963)*. Gutt. [illegible] rot. A solution of silver protein 5%, with phe[illegible] acetate or nitrate 0.002%, in water. Prepared [illegible] ving, aseptically, the silver protein in a [illegible] solution of phenylmercuric acetate or nitrate [illegible] ferring to the final sterilised container. The [illegible] must be freshly prepared. They are advers[illegible] by alkali. Protect from light.

Proprietary Names
Stillargol *(Mayoly-Spindler, Fr.)*.

5323-b

Mild Silver Protein *(B.P.C. 1968)*. Argento[illegible] Mite; Argentum Vitellinicum; Mild Silver Pro[illegible] Silver Nucleinate; Silver Vitellin; Mild Protar[illegible] nato de Plata; Vitelinato de Prata.

NOTE. The name Mild Silver Protein is giv[illegible] compound because it is less bactericidal and [illegible] than Silver Protein, though it contains more [illegible]

Pharmacopoeias. In *Arg., Belg., Fr., Ind.,* [illegible] *Roum., Span., Swiss*, and *Turk.*

A hydroscopic brown powder or nearly black [illegible] granules with a slight odour and taste, contain[illegible] 23% of Ag.
Soluble slowly but completely in water; [illegible] soluble in alcohol, chloroform, and ether. After [illegible] to light it is incompletely soluble in water. [illegible] solution in water is iso-osmotic with serum. [illegible] with cocaine hydrochloride, but compatible [illegible] atropine sulphate solution. Incompatible with [illegible] acids, alkalis, tannins, and oxidising agents. [illegible] airtight containers. Protect from light.

Preservative for eye-drops. Phenylmercuric [illegible] 0.005% was a suitable preservative for mi[illegible] protein eye-drops sterilised by heating at 98[illegible] for 30 minutes.— M. Van Ooteghem, *Pharm. T*[illegible] *Belg.*, 1968, *45*, 69.

Adverse Effects, Treatment, and Precautions. [illegible] Silver (above).

Argyria. Argyria developed in an elderly [illegible] prolonged use of mild silver protein 10% nasal [illegible] W. A. Parker, *Am. J. Hosp. Pharm.*, 1977, 34, [illegible]

Uses. Mild silver protein solutions have anti[illegible] properties similar to those of silver protein solu[illegible] they contain even lower concentrations of ion[illegible] and are consequently less irritant to the tis[illegible] silver protein may be used, therefore, in higher [illegible] trations than silver protein, particularly whe[illegible] important to avoid irritation of mucous me[illegible] Mild silver protein, usually 1 to 5%, is used [illegible] rine as drops or as a spray in nasal infectio[illegible] been applied as a 20% solution in conjunctivit[illegible] the prophylaxis of ophthalmia neonatorum and [illegible] solution to corneal ulcers.

Rhinitis. Mild silver protein (Argyrol) has been [illegible] many years in children with chronic purulent [illegible] and has some value in encouraging nose blo[illegible] main disadvantage is the irreversible staining [illegible] kerchiefs and pillows.— D. F. N. Harrison, *Pre*[illegible] *J.*, 1976, *16*, 69.

Preparations

Mild Silver Protein Eye-drops *(B.P.C. 1963)*. [illegible] Argentoprot. Mit. A solution of mild silver pro[illegible] with phenylmercuric acetate or nitrate 0.002% [illegible] Prepared by dissolving, aseptically, the mil[illegible] protein in a sterile 0.002% solution of pheny[illegible] acetate or nitrate and transferring to the final [illegible] container. The eye-drops must be freshly prep[illegible] are adversely affected by alkali. Protect from lig[illegible] *A.P.F.* (Mild Silver Protein Eye-Drops) has [illegible] protein 20% and phenylmercuric nitrate 0.002[illegible] Water for Injections.

Silver Protein and Ephedrine Instillation *(A.P.F.)*. [illegible] Protein and Ephedrine Nasal Drops. Mild silver [illegible] 5 g, ephedrine 500 mg, phenylmercuric nitra[illegible] freshly boiled and cooled water to 100 ml. This [illegible] should be recently prepared. Protect from light.

Proprietary Preparations

Argotone *(Rona, UK)*. Contains mild silver pr[illegible] and ephedrine hydrochloride 0.9% in 0.5[illegible] chloride solution, available as **Nasal Drops** [illegible] **Ready-Spray** nasal spray in plastic atomisers. [illegible]

Other Proprietary Names
Argincolor *(Fr.)*; Argirol *(Spain)*; Vitargénol *(Fr.)*[illegible]

ighly with hot 3 per cent hydro-
eight of the precipitate so obtained
n.
er Iodide in tight, light-resistant

TRATE SOLUTION

mmoniacal Silver Nitrate, Howe

a solution of silver diammino
equivalent of not less than 28.5
and not less than 9.0 Gm. and

. . . . .	704 Gm.
. . . . .	245 ml.
. . . . .	680 ml.
. . . . .	1000 ml.

ortar and dissolve it in the puri-
l t om temperature and add
e all but the last trace of
his last trace of precipitate from

ion is a clear, colorless, almost odorless
ected by light. Its specific gravity is

ate Solution (1 in 10) responds to the
ate, page 683.
Solution add a few drops of formalde-
recipitate is immediately formed (*dis-
monium nitrates*).
Silver Nitrate Solution (1 in 10) add
filter, add 5 ml. of sodium hydroxide
itmus blue.
remains free from even a transient blue

niacal Silver Nitrate Solution add 3 ml.
the clear filtrate tested in a flame on a
of sodium or potassium (*distinction from*

ml. of Ammoniacal Silver Nitrate Solu-
water, 10 ml. of diluted nitric acid, and
rate with 0.1 *N* ammonium thiocyanate.
is equivalent to 10.79 mg. of Ag.
ut 1 ml. of Ammoniacal Silver Nitrate
e sample to a Kjeldahl distillation flask

with 50 ml. of water, and add sufficient of the water to make a volume of 200 ml.; add 10 ml. of sodium sulfide T.S. and 20 ml. of a solution of sodium hydroxide (4 in 10). Connect the flask to a condenser, the lower outlet tube of which dips beneath the surface of 50 ml. of 0.5 *N* sulfuric acid contained in a receiving flask. Distil the mixture until about 100 ml. of distillate has been collected, add methyl red T.S., and titrate the excess acid with 0.5 *N* sodium hydroxide. Each ml. of 0.5 *N* sulfuric acid is equivalent to 8.516 mg. of NH_3.

The ratio between the percentage of ammonia and the percentage of silver closely approximates 1 to 3.16.

Packaging and storage—Preserve Ammoniacal Silver Nitrate Solution in small glass-stoppered, light-resistant containers, or in light-resistant ampuls.

FOR TOPICAL USE—Mix Ammoniacal Silver Nitrate Solution with a reducing agent, such as formaldehyde (1 in 10) or eugenol, to deposit the metallic silver, in a state of fine subdivision, in the desired area of the tooth.

CATEGORY—Protective (dental).

Silver Protein, Mild

MILD SILVER PROTEIN

Argentum Proteinicum Mite — Mild Protargin

Mild Silver Protein is silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19 per cent and not more than 23 per cent of Ag.

Caution: Solutions of Mild Silver Protein should be freshly prepared or contain a suitable stabilizer, and should be dispensed in amber-colored bottles!

Description—Mild Silver Protein occurs as dark brown or almost black, shining scales or granules. It is odorless, is frequently hygroscopic, and is affected by light.

Solubility—Mild Silver Protein is freely soluble in water, but almost insoluble in alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all carbonaceous matter is burned off, warm the residue with 1 ml. of nitric acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid: a white precipitate is produced which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100) discharges the dark color and a precipitate is gradually produced.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of mercury bichloride T.S.: a white precipitate is formed and the supernatant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 Gm. of Mild Silver Protein in 10 ml. of water. Add, all at once, 7 Gm. of ammonium sulfate, and stir occasionally for 30 minutes. Filter through quantitative filter paper into a 50-ml. Nessler tube, returning the first portions of the filtrate to the filter, if necessary, to secure a clear filtrate, and allow the filter and precipitate to drain. Add to the clear filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube dissolve 7 Gm. of ammonium sulfate in 10 ml. of water, and add to this solution 25 ml. of the solution of acacia and 1.6 ml. of 0.01 *N* silver nitrate. To each tube

Database: Medline <1966 to present>

<1>
Unique Identifier
83203583
Authors
Isenberg S. Apt L. Yoshimuri R.
Title
Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution.
Source
Archives of Ophthalmology. 101(5):764-5, 1983 May.
Abstract
Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

<2>
Unique Identifier
83142687
Authors
Apt L. Isenberg S.
Title
Chemical preparation of skin and eye in ophthalmic surgery: an international survey.
Source
Ophthalmic Surgery. 13(12):1026-9, 1982 Dec.
Abstract
We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver

protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Chemical Preparation of Skin and Eye in Ophthalmic Surgery: An International Survey

Leonard Apt, M.D.
Sherwin Isenberg, M.D.

SUMMARY

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Since the studies of Carl Eberth in 1875, surgeons have known that bacteria are found in hair follicles, sweat glands, and in both the superficial and deeper layers of the skin.[1] Joseph Lister's carbolic acid in spray form, or soaked in gauze and laid on the skin, was the first attempt at preoperative antisepsis. Subsequently, other techniques for achieving preoperative asepsis of the operative field have evolved.

Today, in the course of training in ophthalmic surgery, or when visiting different institutions, one often sees different techniques in preoperative chemical preparation of the eye. The main reasons given for using a certain regimen are tradition and the impression of effectiveness. A scientific rationale rarely is mentioned. To learn the preferences of many ophthalmologists throughout the world, and to determine whether a consensus on a specific regimen exists, we undertook a survey. This information is not found in the ophthalmic literature. The survey was not intended to answer questions definitively about the best method and choice of agents.

MATERIALS AND METHODS

Questionnaires were mailed to 221 ophthalmologists of which 214 were answered and returned. This return rate is 96.8%. In order to obtain a representative sample, ab half of the questionnaires were sent to well-kno ophthalmic surgeons at academic institutions and hal prominent private practitioners of ophthalmology. percent of the questionnaires were answered by wid known ophthalmic surgeons from such foreign countries Mexico, Belgium, Japan, Argentina, Canada, Germa Great Britain, and Switzerland.

The first series of questions asked concerned sequence of solutions applied to the skin, the duration application, and the area of the face receiving application. The second series of questions dealt v solutions intentionally placed on the conjunctiva, durat of application, and what was used as the rinsing agent. third question asked what proportion of the preparat was done by a physician, nurse, or other nonphysic Finally, additional comments were requested.

RESULTS

There was considerable disparity in the types sequence of agents placed on the skin (Table 1). Howe 67.5% of the respondents used povidone-iodine produ (as Betadine, Isodine, Prepodyne, Septodyne) somewh in the preparation, while hexachlorophene (pHisoHex) used by 16.5%, and aqueous iodine solution was used 12.6% somewhere in the preparation. The most frequ regimen of all, used by a third of the respondents, povidone-iodine solution on the skin followed by a rins alcohol. The term "rinse" includes saline, sterile wa lactated Ringer solution, balanced salt solution, or sim product (Figure 1). Half of the respondents used a sin

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TABLE 1

ROUTINE OF CHEMICAL AGENTS
USED FOR SKIN PREPARATION
(n=196)

Multiple Agents	Percent
Povidone-iodine soap → rinse* → Povidone-iodine solution ± alcohol	15.0
Soap → rinse → Povidone-iodine solution ± rinse or alcohol	7.3
Hexachlorophene ± alcohol or rinse → Povidone-iodine ± alcohol or rinse	7.3
Soap ± rinse ± alcohol ± rinse	4.0
Soap ± rinse ± Iodine ± alcohol	3.9
Hexachlorophene → rinse → Iodine ± alcohol	2.4
Hexachlorophene → rinse → merthiolate	1.5
Povidone-iodine → rinse → Iodine	1.0
Alcohol → Povidone-iodine	1.0
Single Agents → Rinse or Alcohol	
Povidone-iodine	32.5
Iodine 1%	4.8
Hexachlorophene	4.3
Zephiran	2.9
Chlorhexidene 1%	2.4
Merfen	1.0
Merthiolate	1.0
Alcohol	1.0
Don't know	1.0

Rinse = saline solution, sterile water, lactated Ringer solution, balanced salt solution, or similar product.

TABLE 2

CHEMICAL AGENTS INTENTIONALLY PLACED
ON THE CONJUNCTIVA
(n=206)

Chemical Agent	Percent
Normal Saline	34.5
Nothing	26.7
Argyrol ± rinse	22.3
Balanced salt solution	5.3
Betadine solution (diluted)	2.4
Neosporin ± rinse	2.0
Ringer solution	1.5
Chlorhexidine	1.0
Sterile water	1.0
Chloramphenicol	1.0
Mercury bichloride	1.0
Gentamycin	0.5
Gentamycin mix	0.5
Don't know	0.5

8 deferred or did not answer.

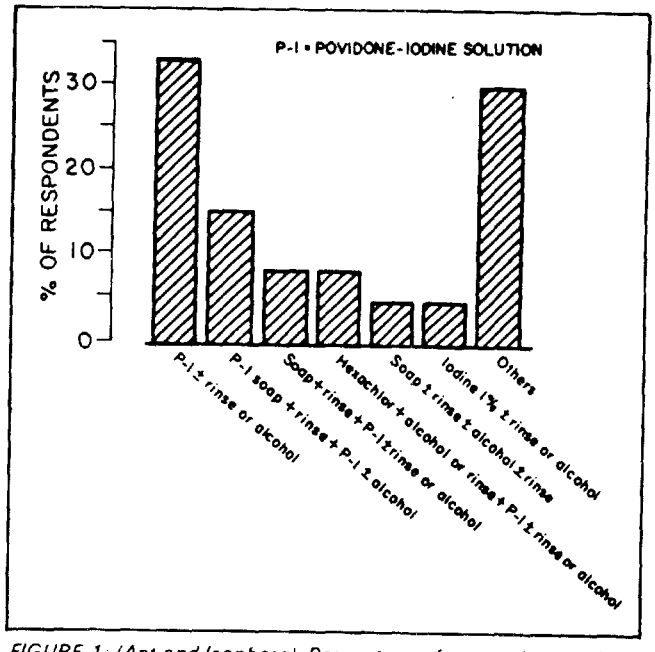

FIGURE 1. (Apt and Isenberg). Percentage of respondents using a particular chemical agent on the skin as part of the preoperative preparation.

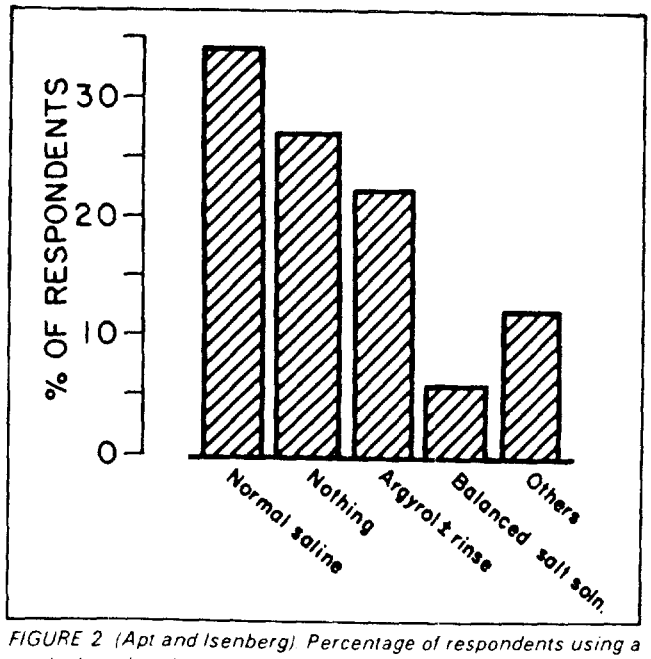

FIGURE 2. (Apt and Isenberg). Percentage of respondents using a particular chemical agent on the conjunctiva as part of the preoperative preparation.

primary agent (such as aqueous iodine, hexachlorophene, or a povidone-iodine product) followed by a rinse or alcohol, while half used a combination of primary agents (Table 1).

The amount of time that these agents were applied to the skin varied from one second to several minutes. So much variation in the length of time was reported as to make

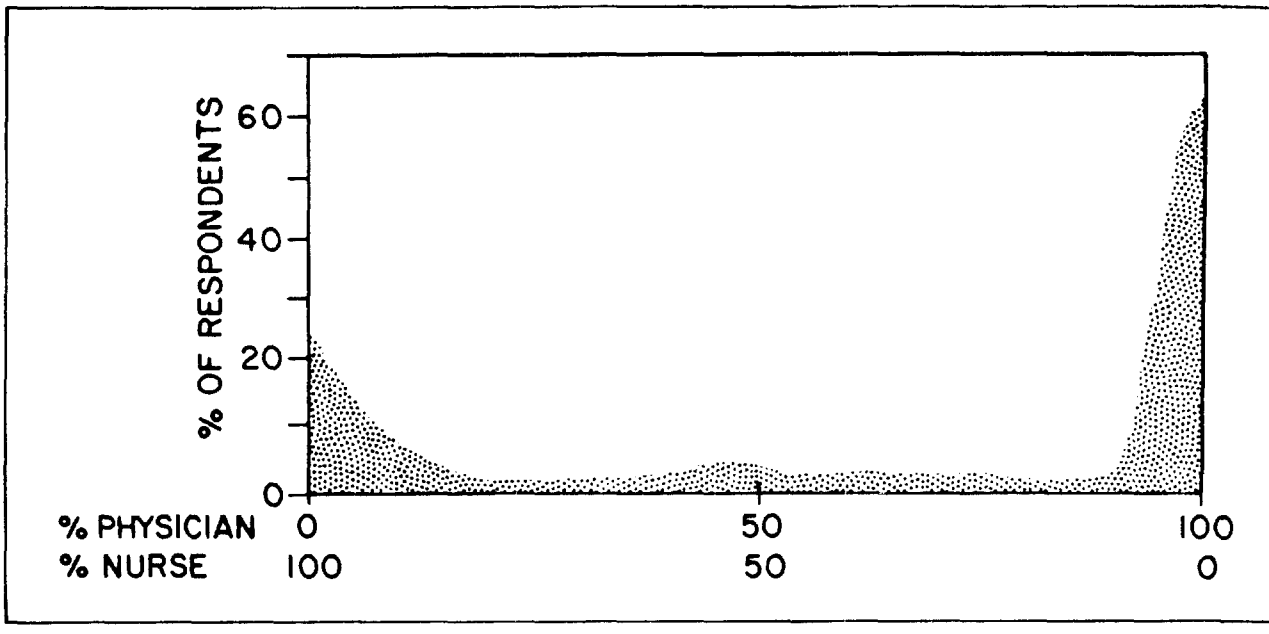

FIGURE 3: (Apt and Isenberg). Relative proportion of physicians compared with nurses performing preoperative preparation of the ey

TABLE 3

HOW MUCH IS DONE BY PHYSICIAN RELATIVE TO NURSE (n=205)

Physician/Nurse	Percent
100%/ 0	62.0
98%/ 2%	0.5
90%/ 10%	0.5
80%/ 20%	1.0
75%/ 25%	1.0
50%/ 50%	2.9
25%/ 75%	1.5
20%/ 80%	0.5
15%/ 85%	0.5
10%/ 90%	4.4
0 100%	29.4
Not known	0.5

9 deferred or did not answer.

conclusions difficult. The facial areas treated were almost universally the forehead, both eyelids, the cheeks, and the nose.

Some ophthalmic surgeons intentionally place solutions on the conjunctiva while others do not (Table 2). About a quarter of the respondents place nothing on the conjunctiva. Forty-two percent simply rinse the conjunctiva with saline solution, balanced salt solution, Ringer solution, or sterile water. Only 31% use a solution bearing any antimicrobial properties. Of the latter, mild silver protein (Argyrol) is by far the most frequently used (Figure 2).

In general, more physicians than nurses perform the preoperative preparation. Sixty-two percent of the res dents indicated that the physician does the entire prep tion, while 29% reported that the nurse does the e preparation. The rest of the respondents answered tha physician and nurse each do part of the preparation (Ta and Figure 3).

COMMENT

The validity of this survey was enhanced by the b spectrum of ophthalmologists contacted, including specialists and general ophthalmologists, academic and nonacademicians, Americans and foreigners, younger and senior ophthalmologists. The highly sati tory rate of returned questionnaires (96.8%) also attes the validity of this survey.

While all ophthalmologists use a form of chen preparation for the eye prior to surgery, there has been recent mention or study of this subject in the ophtha literature. A lack of interest in this subject was exhibit some ophthalmologists who replied that they did not k what agents were used in preparation of the operative To answer this survey, these surgeons had to obtai information from others, usually the surgical nurse. great disparity found in this study in the chemical ag chosen also indicates a lack of recent scientific intere this topic. In 1951, Maumenee and Michler compared different techniques for sterilizing the operative field were then popular.[2] These five techniques were soap saline, either alone or followed by merthiolate or aqu iodine, and hexachlorophene and saline followed by e benzalkonium chloride or aqueous iodine and alcoh our survey, about 11% of the respondents still used o these techniques. The advent of povidone-iodine, experimentally in the 1960s and then clinically in the

70s, changed the techniques of many ophthalmologists.[1-4] In fact, this survey showed that povidone-iodine is currently the single most popular agent for use in chemical preparation of the skin prior to ophthalmic surgery in this country.

Povidone (polyvinylpyrrolidone) is a polymer with surfactant properties that combines easily with iodine. About two thirds of the iodine remains in the elemental state and is slowly released for antibiotic activity. Aqueous solutions of iodine can cause toxicity to the skin and corneal epithelium, and inflammatory changes in the conjunctiva. But if iodine is combined with povidone these problems are less common and of lesser magnitude. Povidone-iodine has been shown to be bactericidal and virucidal in dilute solutions within minutes in vitro.[5] Given the proper concentration and enough contact time, it is effective even against fungi and spores.

There is more consensus among ophthalmologists in regard to the immediate preoperative preparation of the conjunctiva. More than two thirds of the respondents either ignore the conjunctiva or merely irrigate it. Irrigation presumably would remove mucus or other debris, but would not bear any significant antimicrobial action. Only 31% of the reports indicated the use of an antimicrobial agent on the conjunctiva just prior to surgery. However, some ophthalmologists may have used topical antibiotics on the conjunctiva in the days preceding surgery. Whether latter practice truly sterilizes the conjunctiva, or permits active growth of resistant bacteria or regrowth of the original bacteria if a bacteriostatic drug is used, is controversial.[6] Argyrol was the agent most commonly used on the conjunctiva by those who used antimicrobial agents at the time of surgery. Some individuals commented that Argyrol was used because it stains the mucus and other debris, which then can be specifically removed by irrigation, and not necessarily because of its antimicrobial properties.

In reviewing the different combinations of chemicals used to sterilize the skin, some comments of practical importance are indicated. If a soap or scrub is used, either as povidone-iodine, another antimicrobial agent, or simple soap, one should be careful to avoid inadvertent entry of these chemicals onto the conjunctiva. Vascular dilation, hyperemia, and possible corneal damage could result from soap or detergent instillation. Potentially this could lead to more hemorrhage if the conjunctiva is incised. One could place a vasoconstrictor on the conjunctiva before and after the preparation to minimize this problem. Some vasoconstrictors such as phenylephrine will dilate the pupil, while others such as naphazoline will not.

Hexachlorophene is bacteriostatic and is more effective against gram-positive than gram-negative bacteria. It is important to know that a single application of hexachlorophene, as used by some surgeons, has little antimicrobial activity. To be maximally effective, hexachlorophene should be applied at least daily beginning five to seven days prior to surgery. The film of hexachlorophene then produced enhances its antimicrobial effects. Alcohol should not be used to remove the hexachlorophene. Care should be taken to prevent hexachlorophene from entering the palpebral fissure because it is injurious to the corneal epithelium.[7]

It has been noted that benzylkonium chloride is incompatible with iodine and therefore should not be placed in direct contact with it, even on skin.[8] In addition, benzylkonium chloride is inactivated by blood, other organic material, soap, and cotton material which often is used in its application. Ophthalmologists who use multiple agents should reconsider their individual activity with regard to effectiveness, spectrum, and duration of action to avoid overlap.

Some doubt exists as to the efficacy of any preoperative chemical preparation of the eye. Lincoff and coworkers found in one study that an extensive preoperative ophthalmic preparation, including three preoperative soap scrubs, povidone-iodine preparation, saline lavage, and bathing and lavaging implants with chloramphenicol, did not significantly alter their rate of infected scleral implants.[9] In a later study, Hahn, Lincoff, Lincoff, and Kreissig determined that the same organism found on routine intraoperative conjunctival culture was usually the infecting agent in infected scleral implants.[10] They felt that the source of infection was contamination at the site of the buckle operation. Perhaps more emphasis should be placed on sterilization of the conjunctiva. Sterilization of the conjunctiva ultimately might decrease the incidence of infectious endophthalmitis.

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Chemical Preparation of the Eye in Ophthalmic Surgery

II. Effectiveness of Mild Silver Protein Solution

Sherwin Isenberg, MD; Leonard Apt, MD; Robert Yoshimuri, PhD

• **Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.**

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Therapeutic properties of silver and its salts were recognized as early as the Roman Empire period. Jabir ibn Hayyan Geber, an Arabian physician of the eighth century, initiated the use of silver nitrate on the eye.[1] Carl Siegmund Franz Credé began the prophylactic application of silver nitrate on the eyes of newborn infants to prevent gonococcal conjunctivitis in 1884. After that, silver nitrate was used for other ophthalmic disorders, but it was found occasionally to cause necrosis of conjunctival epithelial cells and a gray-black color when light reduced the salt to its metallic state. In addition, irritation, scarring of the conjunctiva, corneal opacification, and symblepharon occurred. In an attempt to reduce these problems, Albert C. Barnes, MD, and Hermann Hille, in 1902, developed a combination of silver nitrate and grain protein (Argyrol).[2] However, this drug also caused complications. In 1980, Spencer et al[3] reported the clinical and histopathologic findings in one patient who drank this mild silver protein solution for years and in a second patient who applied mild silver protein drops to one eye for a long-term period.

A 20% mild silver protein solution is available for topical ocular use in the United States as a silver nitrate and gelatin colloid. The drug is available also abroad under a variety of proprietary names and formulations. It is classified in pharmacy textbooks as a local anti-infective agent.

The antimicrobial properties of this mild silver protein solution have been questioned for years.[4-7] To our knowledge, there has been no controlled clinical study proving the antibiotic efficacy of this mild silver protein solution as part of the chemical preparation of the eye before surgery. Yet, in a recent international survey of ophthalmologists, Apt and Isenberg[8] found that 22% of the respondents use this mild silver protein solution on the conjunctiva as part of the preoperative chemical preparation of the eye. We, therefore, conducted a masked study to investigate the effectiveness of this mild silver protein solution as an antimicrobial agent in the preoperative preparation.

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PATIENTS AND METHODS

Thirty-two patients undergoing ophthalmic surgery were studied. No patient had received preoperative antibiotic therapy or had an active infection at the time of surgery.

All subjects had the identical regimen of preoperative preparation. Initially, a sterile anaerobic transport swab was applied to either the inferonasal or inferotemporal conjunctival fornix of one eye and a second swab was applied to the conjunctiva of the same quadrant in the second eye. Twenty microliters (1 drop) of 20% mild silver protein solution then was instilled in the inferior conjunctival fornix of one randomly selected eye. This eye may have been the eye that was operated on when unilateral ocular surgery was performed. Hexachlorophene soap was applied equally to both eyelids, eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation. Gauze sponges moistened in a saline solution were used to rinse areas bearing hexachlorophene. Next, the quadrant of each inferior conjunctival fornix not previously cultured was cultured with a third and fourth sterile anaerobic transport swab. The choice of which portion of the fornix was cultured before and after the preparation was randomly assigned. Nursing personnel coded each specimen before bacteriologic analysis. The microbiologist had no knowledge of the exact origin of the specimen.

The swab was washed three times in 0.5 mL of Schaedler's broth and wrung out by pressing it along the sides of the tube. The swab was cultured in 10 mL of Schaedler's broth. Blood and chocolate agar each were inoculated with 0.1 mL of eluant and spread on the surface of the agar with a

Table 1.—Mean Number of Colonies and Species of Bacteria Isolated per Subject

	Eye	Mean ± SD: Before Preparation	Mean ± SD: After Preparation	% of Increase
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	Mild silver protein-treated	231 ± 687	323 ± 750	40
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Table 2.—Number of Eyes in Which Culture Was Sterile

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glass rod. The blood agar plates were incubated for seven days at 35 °C in an anaerobic jar with a gas mixture of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. The chocolate agar plates were incubated in 5% to 10% carbon dioxide at 35 °C. After incubation, the colonies were differentiated and enumerated by standard bacteriologic procedures.

RESULTS

Table 1 gives the mean number of colonies and species per subject isolated from untreated and experimental eyes before and after instillation of this mild silver protein solution. Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's *t* test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level.

The pattern of sterile cultures before and after chemical preparation of the eye is given in Table 2. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation.

The organisms cultured were diphtheroids, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Candida albicans*, and *Klebsiella* sp.

COMMENT

This mild silver protein solution originally was intended to be an antimicrobial agent. The colloidal suspension liberates silver ions that alter the protein in the bacterial cell wall. It also has been suggested that silver interferes with essential metabolic activity of bacteria.[4] The silver in this mild silver protein solution ionizes poorly, and thus causes less irritation than silver nitrate. However, its germicidal effectiveness is also decreased. Pharmacologists have written that "colloidal silver preparations are now in a deserved oblivion."[4] Duke-Elder expressed the opinion that this mild silver protein solution has "little bactericidal action since few free ions are liberated."[1] Havener noted that "Argyrol is one of the poorest germicides."[5] None of these authors cited a controlled study on humans to support their assertions. Despite these negative opinions, almost a quarter of the 214 ophthalmologists surveyed in a large international study (with a 96%-response rate) continue to use this mild silver protein solution in the preoperative chemical preparation of the eye.[8] This investigation, using detailed bacteriologic analysis, was unable to verify that the application of this mild silver protein solution on the eye in vivo was significantly better than an untreated eye in reducing the number of microorganisms on the conjunctiva.

Another property of this mild silver protein solution contributes to its popularity. This mild silver protein solution has the capability of darkly staining mucus or debris present on the conjunctiva, eyelids, or skin. It therefore serves as a marker for the adequacy of the preoperative surgical preparation of the eye. The surgeon may then irrigate any remaining mucus and debris from the eye. Indeed, in the international survey by Apt and Isenberg,[8] many respondents commented that they used it mainly to distinguish mucus and debris in the preparation. However, this positive aspect of the tested mild silver protein solution must be weighed against our recent finding that irrigation itself increases the bacterial flora of the conjunctiva (see p 761).

In the design of this study, it was decided to irrigate the conjunctiva of the eye receiving the mild silver protein solution as is commonly practiced. The control eye received no irrigation in light of our aforementioned findings. Thus, any increased degree of antisepsis obtained by the mild silver protein solution may be offset by the increase in bacterial flora engendered by irrigation.

A frequently cited study of the effectiveness of the tested mild silver protein solution and other agents is that of Thompson et al[6] published in 1937. Of the ten bactericidal agents they studied, our tested mild silver protein solution (Argyrol) had the second highest percentage of surviving organisms after one and ten minutes of exposure. Although the investigation by Thompson et al was performed on the conjunctiva of rabbits, doubts about the effectiveness of our tested mild silver protein solution should have been raised at that time. On the human conjunctiva, our study did not find a significant bactericidal effect of this mild silver protein solution when investigated in a masked fashion.

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Chemical Preparation of Skin and Eye in Ophthalmic Surgery: An International Survey

Leonard Apt, M.D.
Sherwin Isenberg, M.D.

SUMMARY

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Since the studies of Carl Eberth in 1875, surgeons have known that bacteria are found in hair follicles, sweat glands, and in both the superficial and deeper layers of the skin.[1] Joseph Lister's carbolic acid in spray form, or soaked in gauze and laid on the skin, was the first attempt at preoperative antisepsis. Subsequently, other techniques for achieving preoperative asepsis of the operative field have evolved.

Today, in the course of training in ophthalmic surgery, or when visiting different institutions, one often sees different techniques in preoperative chemical preparation of the eye. The main reasons given for using a certain regimen are tradition and the impression of effectiveness. A scientific rationale rarely is mentioned. To learn the preferences of many ophthalmologists throughout the world, and to determine whether a consensus on a specific regimen exists, we undertook a survey. This information is not found in the ophthalmic literature. The survey was not intended to answer questions definitively about the best method and choice of agents.

MATERIALS AND METHODS

Questionnaires were mailed to 221 ophthalmologists of which 214 were answered and returned. This return rate is 96.8%. In order to obtain a representative sample, al half of the questionnaires were sent to well-kn ophthalmic surgeons at academic institutions and ha prominent private practitioners of ophthalmology. percent of the questionnaires were answered by wi known ophthalmic surgeons from such foreign countrie Mexico, Belgium, Japan, Argentina, Canada, Germ Great Britain, and Switzerland.

The first series of questions asked concerned sequence of solutions applied to the skin, the duratio application, and the area of the face receiving application. The second series of questions dealt solutions intentionally placed on the conjunctiva, dura of application, and what was used as the rinsing agent. third question asked what proportion of the prepara was done by a physician, nurse, or other nonphysic Finally, additional comments were requested.

RESULTS

There was considerable disparity in the types sequence of agents placed on the skin (Table 1). Howe 67.5% of the respondents used povidone-iodine prod (as Betadine, Isodine, Prepodyne, Septodyne) somew in the preparation, while hexachlorophene (pHisoHex) used by 16.5%, and aqueous iodine solution was use 12.6% somewhere in the preparation. The most freq regimen of all, used by a third of the respondents, povidone-iodine solution on the skin followed by a rins alcohol. The term "rinse" includes saline, sterile w lactated Ringer solution, balanced salt solution, or sir product (Figure 1). Half of the respondents used a si

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TABLE 1

ROUTINE OF CHEMICAL AGENTS
USED FOR SKIN PREPARATION
(n=196)

Multiple Agents	Percent
Povidone-iodine soap → rinse* → Povidone-iodine solution ± alcohol	15.0
Soap → rinse → Povidone-iodine solution ± rinse or alcohol	7.3
Hexachlorophene ± alcohol or rinse → Povidone-iodine ± alcohol or rinse	7.3
Soap ± rinse ± alcohol ± rinse	4.0
Soap ± rinse ± Iodine ± alcohol	3.9
Hexachlorophene → rinse → Iodine ± alcohol	2.4
Hexachlorophene → rinse → merthiolate	1.5
Povidone-iodine → rinse → Iodine	1.0
Alcohol → Povidone-iodine	1.0
Single Agents → Rinse or Alcohol	
Povidone-iodine	32.5
Iodine 1%	4.8
Hexachlorophene	4.3
Zephiran	2.9
Chlorhexidene 1%	2.4
Amerfen	1.0
Merthiolate	1.0
Alcohol	1.0
Don't know	1.0

**Rinse = saline solution, sterile water, lactated Ringer solution, balanced salt solution, or similar product*

TABLE 2

CHEMICAL AGENTS INTENTIONALLY PLACED
ON THE CONJUNCTIVA
(n=206)

Chemical Agent	Percent
Normal Saline	34.5
Nothing	26.7
Argyrol ± rinse	22.3
Balanced salt solution	5.3
Betadine solution (diluted)	2.4
Neosporin ± rinse	2.0
Ringer solution	1.5
Chlorhexidine	1.0
Sterile water	1.0
Chloramphenicol	1.0
Mercury bichloride	1.0
Gentamycin	0.5
Gentamycin mix	0.5
Don't know	0.5

8 deferred or did not answer.

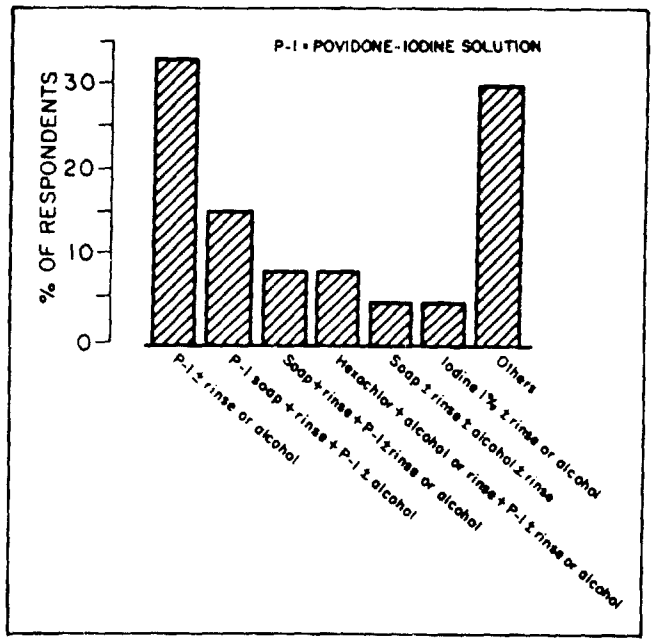

FIGURE 1. (Apt and Isenberg) Percentage of respondents using a particular chemical agent on the skin as part of the preoperative preparation.

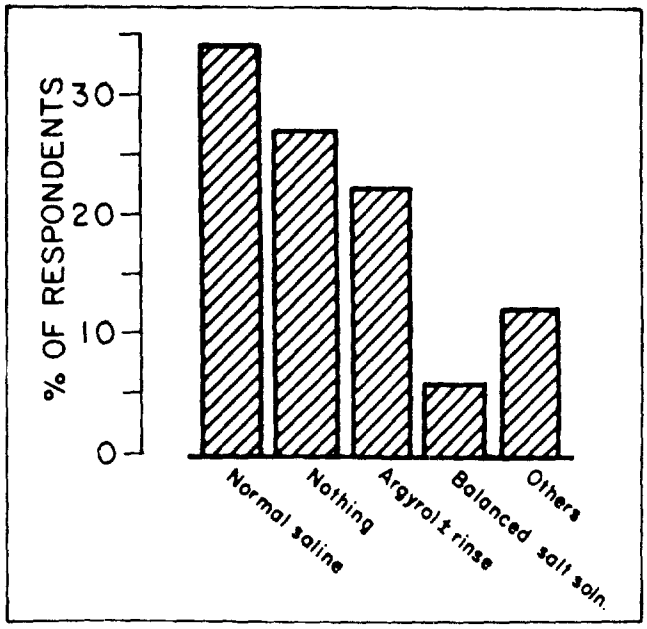

FIGURE 2. (Apt and Isenberg) Percentage of respondents using a particular chemical agent on the conjunctiva as part of the preoperative preparation.

primary agent (such as aqueous iodine, hexachlorophene, or a povidone-iodine product) followed by a rinse or alcohol, while half used a combination of primary agents (Table 1).

The amount of time that these agents were applied to the skin varied from one second to several minutes. So much variation in the length of time was reported as to make

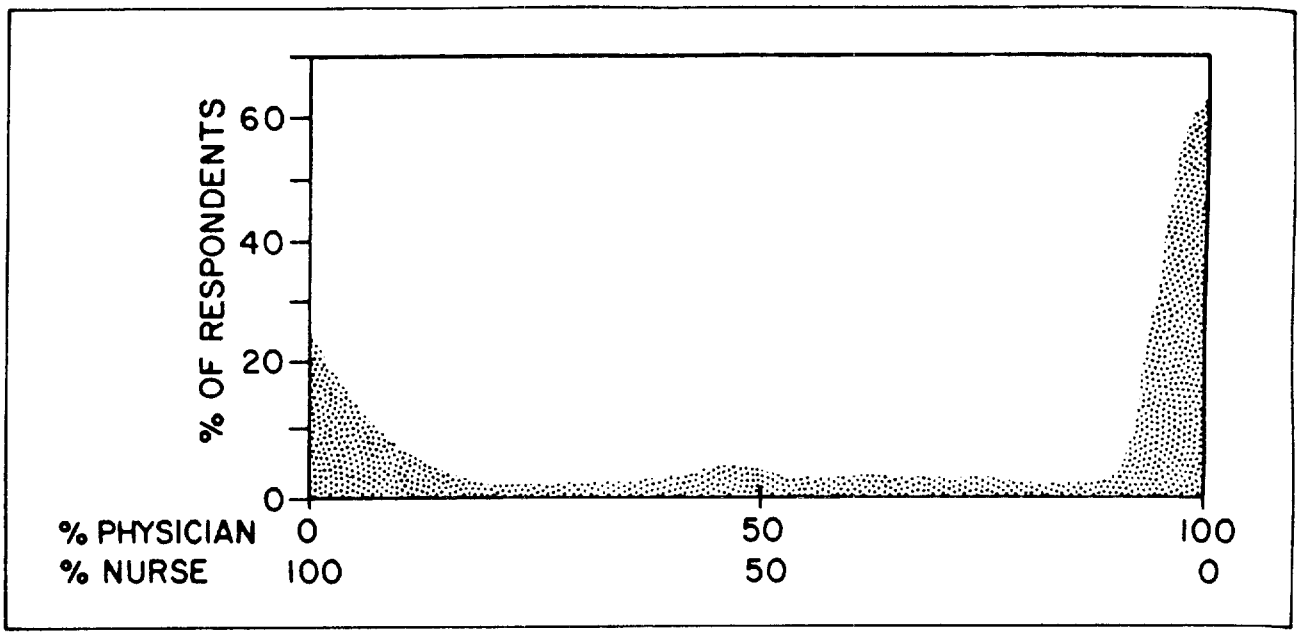

FIGURE 3. (Apt and Isenberg). Relative proportion of physicians compared with nurses performing preoperative preparation of the eye.

TABLE 3

HOW MUCH IS DONE BY PHYSICIAN RELATIVE TO NURSE (n=205)

Physician/Nurse	Percent
100%/ 0	62.0
98%/ 2%	0.5
90%/ 10%	0.5
80%/ 20%	1.0
75%/ 25%	1.0
50%/ 50%	2.9
25%/ 75%	1.5
20%/ 80%	0.5
15%/ 85%	0.5
10%/ 90%	4.4
0 100%	29.4
Not known	0.5

9 deferred or did not answer.

conclusions difficult. The facial areas treated were almost universally the forehead, both eyelids, the cheeks, and the nose.

Some ophthalmic surgeons intentionally place solutions on the conjunctiva while others do not (Table 2). About a quarter of the respondents place nothing on the conjunctiva. Forty-two percent simply rinse the conjunctiva with saline solution, balanced salt solution, Ringer solution, or sterile water. Only 31% use a solution bearing any antimicrobial properties. Of the latter, mild silver protein (Argyrol) is by far the most frequently used (Figure 2).

In general, more physicians than nurses perform the preoperative preparation. Sixty-two percent of the respondents indicated that the physician does the entire preparation, while 29% reported that the nurse does the entire preparation. The rest of the respondents answered that the physician and nurse each do part of the preparation (Table 3 and Figure 3).

COMMENT

The validity of this survey was enhanced by the broad spectrum of ophthalmologists contacted, including subspecialists and general ophthalmologists, academicians and nonacademicians, Americans and foreigners, and younger and senior ophthalmologists. The highly satisfactory rate of returned questionnaires (96.8%) also attests to the validity of this survey.

While all ophthalmologists use a form of chemical preparation for the eye prior to surgery, there has been little recent mention or study of this subject in the ophthalmic literature. A lack of interest in this subject was exhibited by some ophthalmologists who replied that they did not know what agents were used in preparation of the operative field. To answer this survey, these surgeons had to obtain the information from others, usually the surgical nurse. The great disparity found in this study in the chemical agents chosen also indicates a lack of recent scientific interest in this topic. In 1951, Maumenee and Michler compared five different techniques for sterilizing the operative field that were then popular.[3] These five techniques were soap and saline, either alone or followed by merthiolate or aqueous iodine, and hexachlorophene and saline followed by either benzalkonium chloride or aqueous iodine and alcohol. In our survey, about 11% of the respondents still used one of these techniques. The advent of povidone-iodine, first experimentally in the 1960s and then clinically in the early

70s, changed the techniques of many ophthalmologists.[1-4] In fact, this survey showed that povidone-iodine is currently the single most popular agent for use in chemical preparation of the skin prior to ophthalmic surgery in this country.

Povidone (polyvinylpyrrolidone) is a polymer with surfactant properties that combines easily with iodine. About two thirds of the iodine remains in the elemental state and is slowly released for antibiotic activity. Aqueous solutions of iodine can cause toxicity to the skin and corneal epithelium, and inflammatory changes in the conjunctiva. But if iodine is combined with povidone these problems are less common and of lesser magnitude. Povidone-iodine has been shown to be bactericidal and virucidal in dilute solutions within minutes in vitro.[5] Given the proper concentration and enough contact time, it is effective even against fungi and spores.

There is more consensus among ophthalmologists in regard to the immediate preoperative preparation of the conjunctiva. More than two thirds of the respondents either ignore the conjunctiva or merely irrigate it. Irrigation presumably would remove mucus or other debris, but would not bear any significant antimicrobial action. Only 31% of the reports indicated the use of an antimicrobial agent on the conjunctiva just prior to surgery. However, some ophthalmologists may have used topical antibiotics on the conjunctiva in the days preceding surgery. Whether latter practice truly sterilizes the conjunctiva, or permits itive growth of resistant bacteria or regrowth of the original bacteria if a bacteriostatic drug is used, is controversial.[6] Argyrol was the agent most commonly used on the conjunctiva by those who used antimicrobial agents at the time of surgery. Some individuals commented that Argyrol was used because it stains the mucus and other debris, which then can be specifically removed by irrigation, and not necessarily because of its antimicrobial properties.

In reviewing the different combinations of chemicals used to sterilize the skin, some comments of practical importance are indicated. If a soap or scrub is used, either as povidone-iodine, another antimicrobial agent, or simple soap, one should be careful to avoid inadvertent entry of these chemicals onto the conjunctiva. Vascular dilation, hyperemia, and possible corneal damage could result from soap or detergent instillation. Potentially this could lead to more hemorrhage if the conjunctiva is incised. One could place a vasoconstrictor on the conjunctiva before and after the preparation to minimize this problem. Some vasoconstrictors such as phenylephrine will dilate the pupil, while others such as naphazoline will not.

Hexachlorophene is bacteriostatic and is more effective against gram-positive than gram-negative bacteria. It is important to know that a single application of hexachlorophene, as used by some surgeons, has little antimicrobial activity. To be maximally effective, hexachlorophene should be applied at least daily beginning five to seven days prior to surgery. The film of hexachlorophene then produced enhances its antimicrobial effects. Alcohol should not be used to remove the hexachlorophene. Care should be taken to prevent hexachlorophene from entering the palpebral fissure because it is injurious to the corneal epithelium.[7]

It has been noted that benzylkonium chloride is incompatible with iodine and therefore should not be placed in direct contact with it, even on skin.[8] In addition, benzylkonium chloride is inactivated by blood, other organic material, soap, and cotton material which often is used in its application. Ophthalmologists who use multiple agents should reconsider their individual activity with regard to effectiveness, spectrum, and duration of action to avoid overlap.

Some doubt exists as to the efficacy of any preoperative chemical preparation of the eye. Lincoff and coworkers found in one study that an extensive preoperative ophthalmic preparation, including three preoperative soap scrubs, povidone-iodine preparation, saline lavage, and bathing and lavaging implants with chloramphenicol, did not significantly alter their rate of infected scleral implants.[9] In a later study, Hahn, Lincoff, Lincoff, and Kreissig determined that the same organism found on routine intraoperative conjunctival culture was usually the infecting agent in infected scleral implants.[10] They felt that the source of infection was contamination at the site of the buckle operation. Perhaps more emphasis should be placed on sterilization of the conjunctiva. Sterilization of the conjunctiva ultimately might decrease the incidence of infectious endophthalmitis.

REFERENCES

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9. Lincoff H, Nadel A, O'Connor P. The changing character of the infected scleral implant. *Arch Ophthalmol* 1970; 84:421-426.
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A. INGREDIENT NAME:

MYRRH GUM TINCTURE

B. Chemical Name:

C. Common Name:

Myrrha, Gum Myrrh

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

(Test Description)	*(Test Results)*
pH	6.13
Specific Gravity	.8352
Alcohol Content	87.23%
Color	Brownish Red
Odor	Aromatic
Taste	Bitter

E. Information about how the ingredient is supplied:

Brownish red clear volatile liquid, with balsamic-aromatic odor and bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Chil., Ger., Jap., Neth., Port., Span., and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Tian, J. and Shi, S. Constituents of essential oil of imported myrrh and gum opoponax. *Chung Kuo Chung Yao Chih,* 1996; 21(4): 235-237, 256.

H. Information about dosage forms used:

Liquid

I. Information about strength:

2-5ml

J. Information about route of administration:

Apply to indolent ulcers, sore gums, sore mouth, and ulcerated sore throat. Administer internally as a carminative and externally as a protective.

K. Stability data:

L. Formulations:

See compound formula on page 458 to make 1000ml. Please see various lists of formulations in the file.

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

50-1245
#4647C

Item Code: 06151 MYRRH GUM TR NF XI 1:0.2 Lot #: 6-2049

[redacted] 100.0% pure

TEST DESCRIPTION	MINIMUM VALUE	MAXIMUM VALUE	TEST RESULT
pH	4	6.5	6.13
SPECIFIC GRAVITY	.82	.87	.8352
ALCOHOL CONTENT	83%	88%	87.23%
COLOR		BROWNISH RED	BROWNISH RED
ODOR	BALSAMIC/	AROMATIC	AROMATIC
TASTE		BITTER	BITTER

D D

12/96

QUALITY CONTROL REPORT

CHEMICAL NAME.: MYRRH GUM TINCTURE NF

MANUFACTURE LOT NO.: 6-2049

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
BROWNISH RED CLEAR VOLATILE LIQUID; WITH BALSAMIC-AROMATIC ODOR AND BITTER TASTE.

2) SOLUBILITY.:
INSOLUBLE IN WATER; MISCIBLE WITH ALCOHOL.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.: 0.820-0.870.

5) IDENTIFICATION.:
A) A SOLUTION PH IS 5.5.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

ELI LILLY AND -- MYRRH TINCTURE, TT0059
MATERIAL SAFETY DATA SHEET
NSN: 650500N066420
Manufacturer's CAGE: 75602
Part No. Indicator: A
Part Number/Trade Name: MYRRH TINCTURE, TT0059

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General Information

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Company's Name: ELI LILLY AND CO
Company's Street: LILLY CORPORATE CENTER
Company's City: INDIANAPOLIS
Company's State: IN
Company's Country: US
Company's Zip Code: 46285
Company's Emerg Ph #: 317-276-2000;800-424-9300(CHEMTREC)
Company's Info Ph #: 317-276-2286
Record No. For Safety Entry: 001
Tot Safety Entries This Stk#: 001
Status: SMJ
Date MSDS Prepared: 23AUG90
Safety Data Review Date: 14DEC95
MSDS Serial Number: BZRXL

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Ingredients/Identity Information

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Proprietary: NO
Ingredient: RESIN; (S.E. MYRRH). LD50:(ORAL,MOUSE) 13.9 ML/KG.
Ingredient Sequence Number: 01
Percent: 6.6
NIOSH (RTECS) Number: 1000250RE
OSHA PEL: N/K (FP N)
ACGIH TLV: N/K (FP N)

Proprietary: NO
Ingredient: ETHYL ALCOHOL; (ETHANOL). LD50:(ORAL,RAT) 6.9 ML/KG.
Ingredient Sequence Number: 02
Percent: 86
NIOSH (RTECS) Number: KQ6300000
CAS Number: 64-17-5
OSHA PEL: 1000 PPM
ACGIH TLV: 1000 PPM

Proprietary: NO
Ingredient: FIRST AID PROC:DRINK 1-2 GLASSES OF WATER & GIVE 1-2 TBSPS OF SYRUP OF IPECAC TO INDUCE VOMIT/GIVE ANYTHING BY (ING 4)
Ingredient Sequence Number: 03
NIOSH (RTECS) Number: 9999999ZZ
OSHA PEL: NOT APPLICABLE
ACGIH TLV: NOT APPLICABLE

Proprietary: NO
Ingredient: ING 3:MOUTH TO AN UNCONSCIOUS PERSON. IMMEDIATELY TRANSPORT TO MEDICAL CARE FACILITY & SEE MD.
Ingredient Sequence Number: 04
NIOSH (RTECS) Number: 9999999ZZ
OSHA PEL: NOT APPLICABLE
ACGIH TLV: NOT APPLICABLE

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Physical/Chemical Characteristics

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Appearance And Odor: CLEAR, REDDISH-BROWN, HYDROALCOHOLIC SOLUTION; SWEET, PUNGENT ODOR.
Vapor Pressure (MM Hg/70 F): SUPP DATA
Specific Gravity: 0.8344
Evaporation Rate And Ref: NOT APPLICABLE
Solubility In Water: MISCIBLE

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Fire and Explosion Hazard Data

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Flash Point: 153F,67C

Flash Point Method: CC
Extinguishing Media: USE WATER, CO*2, DRY CHEMICAL, FOAM OR HALON.
Special Fire Fighting Proc: USE NIOSH/MSHA APPROVED SCBA & FULL PROTECTIVE EQUIPMENT (FP N).
Unusual Fire And Expl Hazrds: VAPORS ARE HEAVIER THAN AIR & MAY TRAVEL A CONSIDERABLE DISTANCE TO SOURCE OF IGNITION & FLASH BACK. FLAMMABLE (FLASH POINT BELOW 100F, 37.8C).

Reactivity Data

Stability: YES
Cond To Avoid (Stability): STABLE AT NORMAL TEMPERATURES & PRESSURES.
Materials To Avoid: MAY REACT VIOLENTLY W/STRONG OXIDIZING AGENTS, STRONG ACIDS & BASES.
Hazardous Decomp Products: MAY EMIT TOXIC FUMES WHEN HEATED TO DECOMPOSITION.
Hazardous Poly Occur: NO
Conditions To Avoid (Poly): NOT RELEVANT

Health Hazard Data

LD50-LC50 Mixture: SEE INGREDIENTS.
Route Of Entry - Inhalation: YES
Route Of Entry - Skin: YES
Route Of Entry - Ingestion: YES
Health Haz Acute And Chronic: NONE REPORTED, COMPONENTS MAY PRDCE SIGNS & SYMPS AS INDICATED. ETHYL ALCOHOL:INHAL/INGEST OF LG VOLS MAY CAUSE IRRIT OF RESP TRACT, DROW, NAUS, MUSCLE INCOORD, VISUAL IMPAIRMENT, SLOWED RXN TIME, SENSORY LOSS, SLURRING OF SPEECH, STUPOR/POSS COMA & DEATH. BASED ON ANIMAL DATA, MAY BE IRRIT TO EYES & (EFTS OF OVEREXP)
Carcinogenicity - NTP: NO
Carcinogenicity - IARC: NO
Carcinogenicity - OSHA: NO
Explanation Carcinogenicity: NOT RELEVANT
Signs/Symptoms Of Overexp: HLTH HAZ:& SKIN. ANIMAL TOX:ACUTE:INGEST:ING 1:ATAXIA, SEV LETHARGY, DECR BRTHG, LABORED BRTHG, HYPOACTIVITY, HYPERACTIVITY. ING 2:COMA, ATAXIA, LEG WEAK, REDUCED ACTIVITY, CHROMODACRYORRHEA, CHROMORHINORRHEA, CLEAR OCULAR DISCHARGE, SALIVATION, VOCALIZING. INHAL:ING 2:CORNEAL OPACITY, ATAXIA, REDUCED ACTIVITY,(SUPDAT)
Med Cond Aggravated By Exp: ETHYL ALCOHOL - INGESTION, OF LARGE VOLUMES, MAY AGGRAVATE CIRRHOSIS OF LIVER, HYPERSENSITIVITY TO ALCOHOL & GASTROINTESTINAL ABNORMALITIES (PEPTIC ULCERS, GASTRITIS).
Emergency/First Aid Proc: EYES:HOLD EYELIDS OPEN & FLUSH W/STEADY, GENTLE STREAM OF WATER FOR AT LST 15 MINS. SEE OPHTHALMOLOGIST/MD IMMED. SKIN:REMOVE CONTAM CLTHG & CLEAN BEFORE REUSE. WASH ALL EXPOS AREAS OF SKIN W/PLENTY OF SOAP & WATER. GET MED ATTN IF IRRIT DEVELOPS. INHAL:MOVE INDIVIDUAL TO FRESH AIR. IF NOT BRTHG, PROVIDE ARTF RESP ASSISTANCE (MOUTH-TO-MOUTH) & CALL MD IMMED. INGEST:CALL MD/POIS CTL CTR. (ING 3)

Precautions for Safe Handling and Use

Steps If Matl Released/Spill: PREVENT FURTHER MIGRATION INTO ENVIRONMENT. USE ABSORBENT/ADSORBENT MATERIAL TO SOLIDIFY LIQUIDS. SOLIDIFICATION MAY NOT SUPPRESS VAPORS. DO NOT VACUUM LIQUIDS. WEAR PROTECTIVE EQUIPMENT, INCLUDING EYE PROTECTION, TO AVOID EXPOSURE.
Neutralizing Agent: NONE SPECIFIED BY MANUFACTURER.
Waste Disposal Method: MATERIAL IS AN IGNITABLE WASTE UNDER RCRA REGULATIONS. DISPOSE OF ANY CLEANUP MATERIALS & WASTE RESIDUE ACCORDING TO APPLICABLE FEDERAL, STATE & LOCAL REGULATIONS.
Precautions-Handling/Storing: UNDER NORMAL USE & HANDLING CONDITIONS, NO PROTECTIVE EQUIPMENT IS REQUIRED.
Other Precautions: NONE SPECIFIED BY MANUFACTURER.

Control Measures

Respiratory Protection: NIOSH/MSHA APPROVED RESPIRATOR OR LABORATORY FUME HOOD.
Ventilation: LABORATORY FUME HOOD OR LOCAL EXHAUST VENTILATION.
Protective Gloves: IMPERVIOUS GLOVES.
Eye Protection: ANSI APPROVED CHEM WORKERS GOGGS (FP N).
Other Protective Equipment: EYE WASH FOUNTAIN & DELUGE SHOWER WHICH MEET ANSI DESIGN CRITERIA (FP N). BODY COVERING TO PREVENT SKIN CONTACT.
Work Hygienic Practices: NONE SPECIFIED BY MANUFACTURER.

Suppl. Safety & Health Data: VP:2.3 LB/SQ IN. EFTS OF OVEREXP:LOC IRRIT. SKIN/EYE:ING 2:RABBIT, IRRIT. CHRONIC:TARGET ORGAN EFTS:ING 2:CORNEAL DMG, ING 2:TERATOGENIC EFTS HAVE INCL GROWTH RETARDATION, IMPAIRED LEARNING ABILITY & EMBRYOTOXICITY.

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Transportation Data

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Disposal Data

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Label Data

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Label Required: YES
Technical Review Date: 14DEC95
Label Date: 13NOV95
Label Status: G
Common Name: MYRRH TINCTURE, TT0059
Chronic Hazard: NO
Signal Word: WARNING!
Acute Health Hazard-Moderate: X
Contact Hazard-Slight: X
Fire Hazard-Moderate: X
Reactivity Hazard-Slight: X
Special Hazard Precautions: FLAMMABLE. MAY EMIT TOXIC FUMES WHEN HEATED TO DECOMPOSITION. ACUTE:ETHYL ALCOHOL:IRRITATION RESPIRATORY TRACT, DROWSINESS, NAUSEA, MUSCLE INCOORDINATION, VISUAL IMPAIRMENT, SLOWED REACTION, SLURRED SPEECH, COMA & POSSIBLE DEATH. S.E MYRRH:ATAXIA, SEVERE LETHARGY, DECREASED BREATHING, LABORED BREATHING, HYPO/HYPER ACTIVITY. CHRONIC:NONE LISTED BY MANUFACTURER.
Protect Eye: Y
Protect Skin: Y
Protect Respiratory: Y
Label Name: ELI LILLY AND CO
Label Street: LILLY CORPORATE CENTER
Label City: INDIANAPOLIS
Label State: IN
Label Zip Code: 46285
Label Country: US
Label Emergency Number: 317-276-2000;800-424-9300(CHEMTREC)

cyanate, or volatile mustard oil. This reaction takes place at ordinary temperature, and explains the pungent odor and taste of aqueous mixtures of ground mustard.

Description—The N. F. provides a description of *Unground* and *Powdered Black Mustard* and *other seeds or other foreign organic matter* and tests for *Purity*.
Assay—A coarsely powdered sample is macerated with water whereby the sinigrin is hydrolyzed. The liberated allyl isothiocyanate is distilled, with the aid of alcohol, into a mixture of ammonia T.S. and excess standard silver nitrate solution. The ester combines with ammonia to form thiosinamine [$H_2NCSNHC_3H_5$] which subsequently decomposes to allyl cyanamide and hydrogen sulfide, the silver nitrate forming with the latter a precipitate of silver sulfide. After filtering, a portion of the filtrate is acidified with nitric acid and the surplus standard silver nitrate solution is measured by titration with standard ammonium thiocyanate, using ferric ammonium sulfate as the indicator. See page 1458.

Uses—It is used as a *condiment*, *stimulant*, and *emetic;* externally, it is *rubefacient*. When Brown Mustard is prepared as a condiment by the addition of vinegar, salt, and water, the product is known as *German Prepared Mustard*. Both white and black mustard are used in making homemade poultices. It is chiefly used as a counterirritant in the form of "mustard plasters," made by mixing it with varying amounts of wheat flour and adding sufficient tepid water to make a paste. It is occasionally used as a gastric and intestinal stimulant. It is an active, although unpleasant emetic, in a usual dose of 10 Gm.

Dose—*Usual, Emetic*, 10 Gm.

Veterinary Doses—*Carminative* and *stomachic, Horses* and *Cattle*, 8 to 15 Gm.; *Emetic, Dogs*, 4 to 15 Gm. in warm water.

Mustard Plaster N. F.

[Emplastrum Sinapis; Mustard Paper; *Sp.* Emplasto de Mostaza]

Mustard Plaster is a uniform mixture of powdered black mustard, deprived of its fixed oil, and a solution of a suitable adhesive, spread on paper, cotton cloth, or other suitable backing material. Each 100 square centimeters of spread plaster contains not less than 2.5 Gm. of black mustard which has been deprived of its fixed oil.

When moistened thoroughly with tepid water and applied to the skin, the Plaster produces a decided warmth and reddening of the skin within 5 minutes.

Hot water would destroy the enzyme *myrosin* and would not permit the development of the volatile mustard oil to which the rubefacient action is due.

Storage—Preserve in well-closed containers, preferably at a temperature not above 35°. Protect it from direct sunlight.

Uses—A *rubefacient*. A common substitute for the manufactured Mustard Plasters is the *mustard poultice* of the home, usually prepared by mixing equal parts of ground mustard and flour, moistening with tepid water to form a paste, and applying to the skin in a muslin bag.

Note—Before it is applied, Mustard Plaster should be thoroughly moistened with tepid water.

MYRRH N. F.

[Gum Myrrh; *Sp.* Mirra]

Myrrh is the oleo-gum-resin obtained from *Commiphora molmol* Engler, *Commiphora abyssinica* (Berg) Engler, or from other species of *Commiphora* Jacquin (Fam. *Burseraceæ*). Myrrh yields not less than 30 per cent of alcohol-soluble extractive.

Constituents—Myrrh contains from 27 to 50 per cent of *resin*, from 40 to 60 per cent of *gum*, from 2.5 to 10 per cent of *volatile oil*, and a bitter principle. The resin contains *α-*, *β-*, and *γ-commiphoric acids*, the first two having the formula $C_{14}H_{18}O_4$ and the latter $C_{17}H_{22}O_5$; *commiphorinic acid* (believed to be present as the ester); *α-* and *β-heerabomyrrolic acids;* the resin phenols *α-* and *β-heerabomyrrhol;* and *heeraboresene*.

The volatile oil contains up to 24 per cent of two sesquiterpenes, about 11 per cent of *dipentene*, *d-limonene*, 1 per cent of *pinene*, 0.2 per cent of *eugenol*, up to 1 per cent of *cuminic aldehyde*, *cinnamic aldehyde*, and up to 1 per cent of *m-cresol*. *Acetic*, *palmitic*, and *myrrholic acids* are present as esters.

The gum present in the drug has been stated to contain 14 per cent of *pentosans*, 12 per cent of *galactan*, a considerable amount of *xylan*, some *araban*, and an oxidizing enzyme.

Description—The N. F. provides a description of *Unground and Powdered Myrrh* and tests for *Identification* and *Purity*.

Uses—Myrrh is used as a local *stimulant* in diseases of the mouth and as an application for sore gums. It is administered internally as a *carminative* and externally as a *protective*. The volatile oil is used in perfumes of the oriental type and as a fixative.

Myrrh Tincture N. F.

[*Sp.* Tintura de Mirra]

Myrrh, in moderately coarse powder...	200 Gm.
To make.....	1000 ml.

Prepare a tincture by Process M (page 375), using alcohol as the menstruum.

Alcohol Content—From 83 to 88 per cent of C_2H_5OH.
Storage—Preserve in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

Uses—A local stimulant application to *indolent ulcers, sore gums, sore mouth*, and ulcerated *sore throat*.

Dose—*Usual*, 2 ml.

PERUVIAN BALSAM N. F.

[Peru Balsam; Balsam of Peru; Indian Balsam; Black Balsam; *Sp.* Bálsamo Negro; Bálsamo del Perú]

Peruvian Balsam is obtained from *Myroxylon Pereiræ* (Royle) Klotzsch (Fam. *Leguminosæ*).

Constituents—This Balsam contains from 60 to 64 per cent of a volatile oil termed *cinnamein* and from 20 to 28 per cent of *resin*. The higher the content of volatile oil, the greater is the market price of the drug. Cinnamein is a mixture of numerous compounds, among which the following have been identified: the esters *benzyl benzoate*, *benzyl cinnamate*, *cinnamyl cinnamate* (*styracin*), and the alcohol *peruviol* (considered by some authorities to be identical with the sesquiterpene alcohol *nerolidol*, $C_{15}H_{26}O$) as ester; free *cinnamic acid;* about 0.05 per cent of *vanillin;* and a trace of *coumarin*. The presence of the following compounds has also been claimed: *dihydrobenzoic acid*, *farnesol* (a sesquiterpene alcohol), *styrol* (*phenylethylene*), and a *phytosterol*. The resin consists of the benzoic and cinnamic acid esters of the alcohol *peruresinotannol*, together with some free cinnamic acid.

Description—Peruvian Balsam is a dark brown, viscid liquid. It is transparent and appears reddish brown in thin layers. It has an agreeable odor resembling vanilla, a bitter, acrid taste, with a persistent after-taste, and is free from stringiness or stickiness. It does not harden on exposure to air. Specific gravity 1.150 to 1.170. The N. F. provides tests for *Purity*.

Solubility—The Balsam is nearly insoluble in water, but is soluble in alcohol, in chloroform, and in glacial acetic acid, with not more than an opalescence. It is only partly soluble in ether and in solvent hexane.

Storage—Preserve in tight containers and avoid exposure to excessive heat.

seconds was positive, a faint blue colour in 30 seconds was a trace, and no colour was a negative result. The sensitivity of this test was equivalent to the orthotolidine test (orthotolidine 400 mg in glacial acetic acid), and the tablet test (Hematest).—R. H. Wilkinson and W. A. F. Penfold (letter), *Lancet*, ii/1969, 847. Comment.—J. Runcie and T. J. Thomson (letter), ibid., 954. See also ibid., i/1970, 819.

The guaiacum resin and 1% orthotolidine tests for occult blood in faeces produced a high number of false positive results in normal infants and normal children eating a meat-containing diet. A modified reduced phenolphthalein test gave no false positives but was insensitive to blood dilutions below 1 in 5000.—A. E. A. Ford-Jones and J. J. Cogswell, *Archs Dis. Childh.*, 1975, *50*, 238.

PREPARATIONS

Ammoniated Guaiacum Tincture (*B.P.C.* 1949). Tinct. Guaiac. Ammon. Macerate guaiacum resin 20 g with strong ammonia solution 7.5 ml and alcohol (90%) 70 ml for 48 hours; filter, and dissolve in the filtrate, nutmeg oil 0.3 ml and lemon oil 0.2 ml; pour sufficient alcohol (90%) through the filter to produce 100 ml. *Dose:* 2 to 4 ml.

Guaiacum Tincture (*B.P.C.* 1934). Tinct. Guaiac. 1 in 5 of guaiacum resin: prepared by macerating with alcohol (90%) for 48 hours and filtering. *Dose:* 2 to 4 ml.

Guaiacum Wood (*B.P.C.* 1949). Guaiaci Lignum; Lignum Vitae; Bois de Gaiac; Guajakholz. The heartwood of *Guaiacum officinale* and of *G. sanctum* (Zygophyllaceae), containing 18 to 25% of guaiacum resin. It is the source of guaiacum resin and is an ingredient of compound sarsaparilla decoction.

Mastic (*B.P.C.*). Mastiche; Mastix; Almáciga.

Foreign Pharmacopoeias: In *Aust., Neth., Port., Span.*, and *Swiss.*

A resinous exudation from certain forms or varieties of *Pistacia lentiscus* (Anacardiaceae). Small, hard, yellowish tears with an aromatic odour and agreeable taste, becoming plastic when chewed. M.p. 105° to 120°.

Insoluble in water; partly soluble in alcohol and turpentine oil; soluble 2 in 1 of chloroform, 2 in 1 of ether, and in acetone and benzene.

Uses. Solutions of mastic in alcohol, chloroform, or ether are used, applied on cotton wool, as temporary fillings for carious teeth. Compound Mastic Paint is used as a protective covering for wounds and to hold gauze and radium needles in position.

PREPARATIONS

Compound Mastic Paint (*B.P.C.*). Pigmentum Mastiches Compositum; Benzo-mastic; Mastic Solution. Mastic 40 g, castor oil 1.25 ml, benzene, nitration grade of commerce (BS 135/2: 1963), to 100 ml. Store in a cool place in an airtight container. This preparation is inflammable. Keep away from an open flame.

Several foreign pharmacopoeias include similar preparations, usually containing about 30% of mastic and with 1 to 2% of linseed oil instead of castor oil.

Microscopic Varnish. Mastic 15 g, caoutchouc 1 g, chloroform 60 ml; macerate and filter.

Myrrh (*B.P.C.*). Myrrha; Gum Myrrh.

Foreign Pharmacopoeias: In *Aust., Belg., Chil., Ger., Jap., Neth., Port., Span.*, and *Swiss.*

An oleo-gum-resin obtained from the stem of *Commiphora molmol* and possibly other species of *Commiphora* (Burseraceae). Reddish-brown or reddish-yellow tears, with an aromatic odour and a bitter acrid taste. It contains 25 to 40% of resin, 57 to 61% of gum, 7 to 17% of volatile oil, and a bitter principle.

Soluble in water to the extent of about 50% (forms a yellowish emulsion on trituration); partly soluble in alcohol; soluble in alkalis. **Store** in a cool dry place.

Uses. Myrrh is astringent to mucous membranes; the tincture is used in mouth-washes and gargles for ulcers in the mouth and pharynx. When taken by mouth it has a carminative action.

PREPARATION

Myrrh Tincture (*B.P.C.*). Prepared by macerating myrrh 1 in 5 of alcohol (90%). *Dose:* 2.5 to 5 ml.

A similar tincture is included in several foreign pharmacopoeias.

Peru Balsam (*B.P.C.*). Bals. Peruv.; Peruvian Balsam; Baume du Pérou; Baume du San Salvador.

Foreign Pharmacopoeias: In *Arg., Aust., Belg., Braz., Chi... Hung., Jap., Jug., Mex., Neth., Nord., Pol., Port., Roum... Swiss.*

A balsam exuded from the trunk of *Myroxylon bal... pereirae* (Leguminosae). It is a dark brown, viscou... an agreeable balsamic odour and a bitter, acrid, bu... containing 49 to 60% of balsamic esters.

Insoluble in water; miscible 1 in 1 of alcohol... addition of more alcohol causing turbidity; solubl... form; partly soluble in ether, glacial acetic acid... petroleum. Water shaken with the balsam only re... of cinnamic acid. Wt per ml 1.14 to 1.17 g.

Toxic Effects. Peru balsam may cause skin sensitisa...

ALLERGIC REACTION. Of 4000 patients subjected to patch... European clinics 4.6% of males and 7.6% of females sho... reactions to Peru balsam 25% in soft paraffin.—H. Band... *Archs Derm.*, 1972, *106*, 335. See also E. Rudzki and D... *Br. J. Derm.*, 1970, *83*, 543.

Uses. Peru balsam has a very mild antiseptic actio... of its content of cinnamic and benzoic acids. Dilut... equal part of castor oil, it has been used as an ap... bedsores and chronic ulcers; as an ointment (12.5... Ointment) it has been used in the treatment of... pruritus. It is an ingredient of some rectal suppos... for the symptomatic relief of haemorrhoids.

Peru balsam was formerly used as an ointment,... or with sulphur, in the treatment of scabies, but... superseded for this purpose by benzyl benzoate.

PREPARATION

Ung. Bals. Peruv. Co. (*B.N.F.* 1957). Peru Balsam Compou... Peru balsam 6, liquefied phenol 2, camphor 1, hydrous... yellow soft paraffin to 100.

Polyvinox. Vinylinum (*Rus.P.*); Polyvinylbutyl Ether; ... Balsam. Poly(butylvinyl ether), $C_{14}H_{24}O_3(C_6H_{12}O)_n = 200$...

A pale yellow, viscous liquid with a characteristic odou... about 0.9 g. **Insoluble** in water; sparingly soluble in... methyl alcohol; miscible with acetone, chloroform, ether, li... and vegetable oils.

A synthetic resin, developed in the USSR as a substitute for... It is widely used in the USSR by external application, either... or as a 20% oily solution or as an ointment, in the t... wounds and burns and various skin diseases. It is state... bacteriostatic action and to promote tissue regeneration and... ation. It is also administered by mouth in the treatment of... duodenal ulcers, gastritis, and colitis. *Dose:* 4 to 8 m... 5 to 6 hours after the last meal.

PROPRIETARY PREPARATION

Shostakovsky Balsam (*Medexport, USSR: Leopold Charle...* polyvinox.

Sandarac (*B.P.C.* 1949). Sandaraca; Gum Juniper.

A resin obtained by incision of the stem of *Tetracli...* (Cupressaceae). Brittle pale yellow tears, which do not aggl... chewed, with a slightly terebinthinate odour and taste... 160°. **Insoluble** in water; soluble in alcohol, amyl alcoho... partly soluble in chloroform, carbon disulphide, and turpe... Sandarac has been used in alcoholic solution, 2 parts of ... 1 of alcohol (90%), on cotton wool, as a temporary fillin... teeth. It is used in pill varnishes and in industrial varnishes...

Pill Varnish. A solution of sandarac 1 in 2 of alcohol (... quicker drying, sandarac 1 in a mixture of alcohol (95%)...

Shellac (*B.P.C.* 1963). Lacca; Lacca in Tabulis.

Foreign Pharmacopoeias: In *Span. Jap.* includes Purified... White Shellac (bleached).

A resinous substance formed by a scale insect, *La...* (Coccidae), which lives on the sap of the stems... plants. Pale lemon-yellow to brownish-orange,... odourless, tasteless, hard, brittle scales. Insolu... readily soluble in warm alcohol; almost completely... alkali hydroxide solutions and borax solutions.

Uses. Shellac is used with cetostearyl alcohol as...

Description—Myrcia Oil occurs as a yel brownish yellow liquid with a pleasant, ar odor, and a pungent, spicy taste.

Solubility—Myrcia Oil yields solution are clear or but slightly turbid with equal vo of alcohol or of glacial acetic acid.

Identification—

A: Mix Myrcia Oil with an equal of a concentrated solution of sodium hydr a semi-solid mass forms.

B: Dissolve 2 drops of Myrcia Oil in of alcohol, and add 1 drop of ferric chlorid a light green color is produced. If the sam is made with 1 drop of dilute ferric chlorid prepared by diluting the test solution volumes of water, a yellow color is pro which soon disappears.

C: Shake 1 ml. of Myrcia Oil with 20 hot water, and filter: the filtrate gives no than a slight acid reaction with litmus, the addition of 1 drop of ferric chlorid yields only a transient grayish green, no or purple color.

Specific gravity—The specific grav Myrcia Oil is not less than 0.950 and no than 0.990.

Optical rotation, page 443—Myrcia levorotatory, but the angle of rotation of in a 100-mm. tube does not exceed −3

Refractive index, page 448—The re index of Myrcia Oil is not less than 1.50 not more than 1.5160 at 20°.

Reaction—An alcohol solution of Myrci o litmus.

y—Introduce exactly 10 ml. of o a cassia flask, add 75 ml. of po hydroxide T.S., stopper the flask tightly the mixture thoroughly, and let it stand night. Then add sufficient potassium hy T.S. to raise the lower limit of the oil within the graduated portion of the nec flask, and, after the alkaline solution has clear, adjust it to the temperature at whi measured, and note the volume of the oily liquid. This volume is not less than and not more than 5 ml., indicating the in Myrcia Oil of not less than 50 per cent more than 65 per cent, by volume, of phe

Packaging and storage—Preserve My in tight, light-resistant containers.

Category—Perfume; pharmaceutica sity; ingredient of Compound Myrcia Sp

Compound Myrcia Spirit

Myrcia Oil	8
Orange Oil	0
Pimenta Oil	0
Alcohol	610
Water, a sufficient quantity,	
To make	1000

Mix the oils with the alcohol and gradually add water until the product measures 1000 ml. Set the mixture aside in a well-closed container for 8 days, and then filter, using 10 Gm. of talc if necessary, to render the product clear.

Alcohol content, page 404—Compound Myrcia Spirit contains from 54 to 59 per cent of C_2H_5OH.

Packaging and storage—Preserve Compound Myrcia Spirit in tight, light-resistant containers.

Category—Perfume.

MYRISTICA

Nutmeg

Myristica is the dried ripe seed of *Myristica fragrans* Houttuyn (Fam. *Myristicaceæ*), deprived of its seed-coat and arillode and with or without a thin coating of lime.

Unground Myristica is ovoid or ellipsoidal and from 20 to 35 mm. in length and from 15 to 28 mm. in width. Externally it is light brown to dark brown. The surface is reticulately furrowed, the broad end with a large, circular, upraised scar from which arises a raphe extending to a depression at the opposite end. The cut surface has a waxy luster and a mottled appearance, given by the dark perisperm and the lighter colored endosperm. The odor is characteristically aromatic and the taste pungently aromatic.

Histology—Myristica perisperm is thin, reddish brown to yellowish orange, penetrating by many wavy branches or folds into the yellowish brown endosperm and forming with it ruminate albumen. The embryo is small and more or less shrunken in an irregular cavity near the base.

Powdered Myristica is brown to moderate yellowish brown and consists of irregular fragments; perisperm with large, circular or elliptical volatile-oil reservoirs, small thin-walled parenchyma cells with reddish orange to orange or brown contents and occasional spiral tracheids and vessels. The endosperm shows more or less polygonal parenchyma cells containing starch, large aleurone grains, fat, and occasionally brown to yellowish orange pigment. Fixed oil globules are numerous, and the starch grains are single or 2- to 3-compound, or in aggregates, the individual grains spherical, planoconvex, or polygonal, from 3 to 22 μ in diameter, with a distinct, sometimes cleft hilum.

Acid-insoluble ash, page 460—Myristica yields not more than 0.5 per cent of acid-insoluble ash.

Nonvolatile ether-soluble extractive, page 462—Myristica yields not less than 25 per cent of nonvolatile ether-soluble extractive.

Packaging and storage—Preserve Myristica in tight containers.

Category—Pharmaceutical necessity; ingredient of Aromatic Rhubarb Tincture, page 313.

MYRRH

Gum Myrrh

Myrrh is the oleo-gum-resin obtained from *Commiphora molmol* Engler, *Commiphora abyssinica* (Berg) Engler, or from other species of *Commiphora* Jacquin (Fam. *Burseraceæ*).

Unground Myrrh—Unground Myrrh occurs in rounded or irregular tears or masses of agglutinated tears, moderate yellow to dark or reddish brown, and more or less covered with a lighter colored, yellowish dust. The fracture is waxy, granular, conchoidal; internally, Myrrh is yellowish or reddish brown, sometimes marked with nearly white spots or lines, oily and translucent at the edges. Its odor is balsamic, aromatic, not terebinthinate, and its taste is aromatic, bitter, and acrid.

Powdered Myrrh is weak yellowish orange to strong yellowish brown and consists of numerous angular fragments of resin and gum, a few fragments of lignified tissue, and a very few starch grains.

Identification—

A: To a portion of Myrrh add nitric acid: a purplish to violet color is produced.

B: Expose an ether solution of Myrrh to bromine vapors: a reddish violet color is produced.

C: Triturate about 1 Gm. of Myrrh with 5 ml. of water: a yellowish to yellowish brown emulsion is produced.

Acid-insoluble ash, page 460—Myrrh yields not more than 5 per cent of acid-insoluble ash.

Alcohol-soluble extractive, page 462—Myrrh yields not less than 30 per cent of alcohol-soluble extractive.

Category—Protective.

Myrrh Tincture

Myrrh, in moderately coarse powder.	200 Gm.
To make	1000 ml.

Prepare a tincture by Process M, page 458, using alcohol as the menstruum.

Alcohol content, page 404—Myrrh Tincture contains from 83 to 88 per cent of C_2H_5OH.

Packaging and storage—Preserve Myrrh Tincture in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

Category—See Myrrh.

Usual dose—2 ml.

TINCTURES

Tinctures are alcoholic or hydroalcoholic solutions prepared from animal or vegetable drugs or from chemical substances.

The proportion of drug represented in the different tinctures is not uniform but varies according to the established standards for each. Tinctures of potent drugs essentially represent the activity of 10 Gm. of the drug in each 100 ml. of tincture. This conforms in principle to the recommendation of the International Protocol as adopted at Brussels, and with international standards. In this group are most of the tinctures which are assayed and adjusted to standards. Most of the other tinctures represent 20 Gm. of the respective drugs in each 100 ml. of tincture. Compound tinctures are made according to long established formulas.

The general processes to be employed for the manufacture of tinctures, unless otherwise directed in the individual monographs, are as follows:

Process P—Carefully mix the ground drug or mixture of drugs with a sufficient quantity of the prescribed menstruum to render it evenly and distinctly damp, allow it to stand for 15 minutes, transfer it to a suitable percolator, and pack the drug firmly. Pour on enough of the prescribed menstruum to saturate the drug, cover the top of the percolator, and when the liquid is about to drip from the percolator, close the lower orifice, and allow the drug to macerate for 24 hours or for the time specified in the monograph. If no assay is directed, allow the percolation to proceed slowly, or at the specified rate, gradually adding sufficient menstruum to produce 1000 ml. of tincture, and mix thoroughly.

If an assay is directed, collect only 950 ml. of percolate; mix this thoroughly, and assay a portion of it as directed. Dilute the remainder with such a quantity of the prescribed menstruum as calculation from the assay indicates is necessary to produce a tincture that conforms to the prescribed standard. Mix well. The rate of flow of percolates is defined on page 428.

Process M—Macerate the drug or mixture of drugs in a container which can be closed, in a moderately warm place, with 750 ml. of the prescribed menstruum, agitating it frequently for 3 days or until the soluble matter is dissolved. Transfer the mixture to a filter, and when most of the liquid has drained away, wash the residue on the filter with a sufficient quantity of the prescribed menstruum, combining the filtrates, to produce 1000 ml. of tincture. Mix the product well.

Packaging and Storage—Preserve Tinctures in tight, light-resistant containers and avoid exposure to direct sunlight and to excessive heat.

TITRIMETRY

Direct Titrations—Direct titration is the treatment of a soluble substance, contained in solution in a suitable vessel, with an appropriate standardized solution (the titrant), the end point being determined potentiometrically or visually with the aid of a suitable indicator added at the appropriate time.

The titrant is added from a suitable buret and is so chosen, with respect to its strength (normality) that the volume added is between 30 per cent and 100 per cent of the rated capacity of the buret. The end point is approached directly but cautiously, and finally the titrant is added dropwise from the buret in order that the final drop added will not overrun the end point. The quantity of the substance being titrated may be calculated from the volume and the normality factor of the titrant and the equivalence factor for the substance given in the individual monograph.

Residual Titrations—Certain National Formulary assays require the addition of a measured volume of a volumetric solution, in excess of the amount actually needed to react with the substance being assayed, the excess of this solution then being titrated with a second volumetric solution. This constitutes a residual titration and is known also as a "back titration." The quantity of the substance being titrated may be calculated from the difference between the volume of the volumetric solution originally added and that consumed by the titrant in the back titration, due allowance being made for the respective normality factors of the two solutions and the equivalence factor for the substance given in the individual monograph.

In many such assays it is further specified that a *residual blank titration* be performed, wherein the required procedure is repeated in every detail except that the substance being assayed is omitted. In such instances, the actual volume of titrant equivalent to the substance being assayed is the difference between the volume consumed in the residual blank titration and that consumed in the titration with the substance present. The corrected volume so obtained is used in calculating the quantity of the substance being titrated, in the same manner as prescribed in the preceding paragraph.

Complexometric Titrations—Simple, direct titrations of some polyvalent cations are possible by use of reagents with which the cations form complexes. The titration of the calcium ion by this means is particularly advantageous, in comparison to the oxalate precipitation methods heretofore used for National Formulary purposes. The success of complexometry depends in large measure upon the indicator chosen. Often, no single indicator is entirely satisfactory. Thus a combination of two indicators may be specified where the complexometric method is applied in this National Formulary.

Titration in Nonaqueous Solvents—Acids and bases have long been defined as substances which furnish, when dissolved in water, hydrogen and hydroxyl ions, respectively. This definition,

which the oils have been dissolved, and *two hundred and fifty mils* of water. Complete the preparation with a mixture of *three volumes* of alcohol and *one volume* of water.

AVERAGE DOSE—Metric, 2 mils—Apothecaries, 30 minims.

TINCTURA LIMONIS CORTICIS

Tincture of Lemon Peel

Tr. Limon. Cort.

LEMON PEEL, grated from the fresh fruit, *five hundred grammes*	500 Gm.
To make *one thousand milliliters*	1000 mils

Prepare a Tincture by Type Process M (see page 445), macerating the drug in *one thousand mils* of alcohol and completing the preparation with alcohol. Use purified cotton as the filtering medium.

TINCTURA LOBELIÆ

Tincture of Lobelia

Tr. Lobel.—Lobeliæ tinctura P.I.

LOBELIA, in No. 50 powder, *one hundred grammes*	100 Gm.
To make *one thousand milliliters*	1000 mils

Prepare a Tincture by Type Process P (see page 444), using diluted alcohol as the menstruum.

AVERAGE DOSE—Metric, 1 mil—Apothecaries, 15 minims.

TINCTURA MOSCHI

Tincture of Musk

Tr. Mosch.

MUSK, *five grammes*	5 Gm.
ALCOHOL, *forty-five milliliters*	45 mils
WATER, *forty-five milliliters*	45 mils
DILUTED ALCOHOL, *a sufficient quantity*,	
To make *one hundred milliliters*	100 mils

Triturate the musk with the water gradually added until a smooth mixture is obtained; transfer this to a bottle and allow the mixture to macerate for twenty-four hours; then add the alcohol and macerate the

ved, and *two hundred and fifty mil*
on with a mixture of *three volume*

2 mils—Apothecaries, 30 minims.

MONIS CORTICIS
of Lemon Peel
mon. Cort.

fresh fruit, *five hundred*
..... 500 Gm
and milliliters ..... 1000 mil

ocess M (see page 445), macerati
ohol and completing the preparati
as the filtering medium.

LOBELIÆ
of Lobelia
eliæ tinctura P.I.

ur[illegible]grammes..... 100 Gm
d [illegible]liters ..... 1000 mil

ss P (see page 444), using dilute

il—Apothecaries, 15 minims.

MOSCHI
f Musk
ch.

..... 5 Gm
..... 45 mil
..... 45 mil
ity,
illiliters..... 100 mil

gradually added until a smooth
bottle and allow the mixture to
ld the alcohol and macerate the

mixture for six days, with occasional agitation. Transfer this mixture to a plain paper filter, and, when the liquid has drained off completely, wash the residue on the filter with sufficient diluted alcohol to make *one hundred mils* of Tincture.

AVERAGE DOSE—Metric, 4 mils—Apothecaries, 1 fluidrachm.

TINCTURA MYRRHÆ
Tincture of Myrrh
Tr. Myrrh.

MYRRH, in moderately coarse powder, *two hundred grammes* 200 Gm.
To make *one thousand milliliters* ..... 1000 mils

Prepare a Tincture by Type Process M (see page 445), using alcohol as the solvent.

AVERAGE DOSE—Metric, 1 mil—Apothecaries, 15 minims.

TINCTURA NUCIS VOMICÆ
Tincture of Nux Vomica
Tr. Nuc. Vom.—Strychni tinctura P.I.

One hundred mils of Tincture of Nux Vomica yields not less than 0.237 Gm. nor more than 0.263 Gm. of the alkaloids of nux vomica.

NUX VOMICA, in No. 40 powder, *one hundred grammes*... 100 Gm.
To make about *one thousand milliliters*..... 1000 mils

Prepare a Tincture by Type Process P, as modified for assayed tinctures (see page 444), using a mixture of *three volumes* of alcohol and *one volume* of water as the menstruum and adjusting the volume of the finished Tincture so that each *one hundred mils* contains 0.25 Gm. of the alkaloids of nux vomica. The rate of flow for the percolate should not exceed ten drops per minute.

Assay—Evaporate 100 mils of Tincture of Nux Vomica on a water bath until it measures about 10 mils, transfer the evaporated liquid to a separator, and proceed as directed in the assay under *Fluidextractum Belladonnæ Radicis*, page 178, second line of the Assay, beginning with the words "add 10 mils," modifying the process there given by using 5 mils of ammonia water with a little distilled water, in divided portions, to rinse the dish in which the Tincture was evaporated and by dissolving the residue in 10 mils of tenth-normal sulphuric acid V.S. instead of 5 mils.

Each mil of tenth-normal sulphuric acid V.S. consumed corresponds to 36.4 milligrammes of the alkaloids of nux vomica.

AVERAGE DOSE—Metric, 0.5 mil—Apothecaries, 8 minims.

Tryparsamide (*B.P.*). $C_8H_{10}O_4N_2AsNa,1\frac{1}{2}H_2O=305{\cdot}1$. It contains 25·1 to 25·5 per cent of arsenic, As, and 9·25 to 9·5 per cent of nitrogen, N, both calculated with reference to the substance dried at 105°; the loss on drying is 2·5 to 3·5 per cent. That of the *U.S.P.* contains arsenic corresponding to 99 to the equivalent of 101 per cent of anhydrous tryparsamide, $C_8H_{10}O_4N_2AsNa$, calculated with reference to the dried substance, determined by the *U.S.P.* method for carbarsone; the loss on drying at 105° for 4 hours is 2·5 to 3·5 per cent. That of the *Fr. Cx.* contains 24·4 to 24·9 per cent of arsenic, determined by the following method:

To about 0·5 g., accurately weighed, dissolved in 45 ml. of water, add 5 ml. of hydrochloric acid and 12·5 g. of potassium iodide, heat on a water-bath for 20 minutes, allow to cool, and titrate with N/10 sodium thiosulphate until decolorised, avoiding any excess; add carefully about 10 g. of sodium bicarbonate, and titrate with N/10 iodine. Each ml. of N/10 iodine is equivalent to 0·003745 g. of arsenic, As.

Injection of Tryparsamide (*B.P.*). In the sealed container is dry powder containing arsenic, As, equivalent to 22·0 to 28·0 per cent, and nitrogen, N, equivalent to 8·0 to 10·5 per cent of the stated amount of tryparsamide, determined by the *B.P.* method for tryparsamide.

Arsine. $AsH_3=77{\cdot}9$.

DETECTION AND DETERMINATION OF ARSINE. The Department of Scientific and Industrial Research Leaflet, 'Methods for the Detection of Toxic Gases in Industry, No. 9' (H.M. Stationery Office) gives details of a method for the detection of arsine in air in which a quantity of air is passed through lead acetate paper (to absorb hydrogen sulphide) and then through mercuric chloride paper. The concentration of arsine is given by the number of strokes of a pump (described in the leaflet) which are required to give the mercuric chloride paper the same colour as that of one of the standard stains.

The Lovibond Comparator may be used in the determination of arsine in air by the method described above.—'Handbook of Colorimetric Chemical Analytical Methods', 3rd Edn, Tintometer Ltd., Salisbury, 1953, p. 161.

ARSINE DERIVATIVES. *Many* cases of poisoning due to wallpapers containing arsenic h[illegible]en reported, and one has been recorded where the wall was composed of coke b[illegible]d cement. In every instance the walls were damp and it has been shown that the li[illegible] of arsenic is due to the action of mould growths and the formation of substi[illegible] arsines, of which the dimethyl-, trimethyl- and diethyl-arsines are the most important. These gases possess a strong odour of garlic and it has been suggested that the production of trimethylarsine by the growth of *Penicillium brevicaule* on media, to which has been added a small quantity of the material to be examined, is as sensitive as the Gutzeit test.

BIOLOGICAL TEST. The addition of a substance containing a trace of arsenic to a growing culture of a *Penicillium* causes in a few minutes an evolution of arsine which can be detected by the smell: 0·0000001 g. of As can be detected.—B. Gosio, *Boll. Ist. sieroter. Milano*, 1932, *11*, 597.

The gas evolved is trimethylarsine.—F. Challenger *et al.*, *J. chem. Soc.*, 1933, 95.

DETERMINATION OF ORGANIC ARSINES. The only organic arsine which is readily decomposed is lewisite and as this may be impure or mixed with another arsenical it is necessary to break down the contaminated material by organic combustion, which converts the arsenic to the arsenical condition, which must be reduced by sulphur dioxide or other process before the arsenic can be determined by the modified Gutzeit process.

ASAFETIDA

Asafetida (*B.P.C. 1949*). It is the oleo-gum-resin obtained from the living rhizome and root of *Ferula fœtida* Regel, *F. rubricaulis* Boiss., or other species of *Ferula*. It may be identified (i) by the bright red or reddish-brown colour produced when the fractured surface is touched with sulphuric acid, changing to violet when the acid is washed off with water, (ii) by the green colour produced when the freshly broken surface is touched with nitric acid (50 per cent v/v), and (iii) by the blue fluorescence produced when asafetida is boiled for some minutes with hydrochloric acid and the solution made alkaline with ammonia solution and diluted. It yields not more than 50 per cent of alcohol (90 per cent)-insoluble matter and not more than 15 per cent of ash. It contains about 6 to 17 per cent of volatile oil, about 40 to 64 per cent of resin, and about 25 per cent of gum. Pure tear asafetida usually contains from 65 to 75 per cent of alcohol (90 per cent)-soluble substances and 3 to 5 per cent of ash. That of the *N.F.-U.S.A.* yields on continuous extraction with alcohol (95 per cent) not less than 50 per cent of alcohol-soluble extractive, calculated on the dried drug, the moisture having been determined by azeotropic distillation with toluene, and not more than 15 per cent of acid-insoluble ash.

ASAFETIDA OIL. The main fraction, b.p. 82° to 84° at 10 mm., is optically active and has a composition corresponding to $CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}S{\cdot}S{\cdot}CH{:}CH{\cdot}CH_3$.—C. Mannich and P. Frensenius, *Arch. Pharm., Berl.*, 1936, *274*, 461, per *Quart. J. Pharm.*, 1936, *9*, 710.

Myrrh (*B.P.C.*). It contains at least 7·0 per cent v/w of volatile oil. That of the *N.F.-U.S.A.* yields not more than 5 per cent of acid-insoluble ash and at least 30 per cent of alcohol (95 per cent)-soluble extractive.

AUROTHIOMALIC ACID

Sodium Aurothiomalate (*B.P.*). It contains 44·5 to 46·0 per cent of gold, Au, determined gravimetrically, and 10·8 to 11·3 per cent of sodium, Na, determined gravimetrically as sodium sulphate, both calculated with reference to the dried substance; the loss on drying over phosphorus pentoxide under reduced pressure for 24 hours is not more than 2·0 per cent.

Injection of Sodium Aurothiomalate (*B.P.*). This solution contains gold, Au, equivalent to 42·3 to 48·3 per cent of the stated amount of sodium aurothiomalate, determined gravimetrically as gold, Au.

Sodium Aurothiosulphate (*B.P.C. 1949*). $Na_3Au(S_2O_3)_2,2H_2O=526{\cdot}5$. It may be identified by adding 2 drops of sodium hydroxide solution and 3 ml. of hydrogen peroxide solution to 3 ml. of a 1 per cent solution, when a blue colour and a deposit of finely divided gold is produced. It contains 37·0 to 37·6 per cent of gold, Au, determined by the following method:

Dissolve 0·8 g. in 50 ml. of water and add 10 ml. of N/1 sodium hydroxide and 10 ml. of hydrogen peroxide solution; boil to decompose the excess of hydrogen peroxide, acidify with hydrochloric acid and allow the precipitate of metallic gold to coagulate; filter, wash with boiling water, dry, ignite, and weigh the residue of gold, Au.

BARBITONE

Barbitone (*B.P.*). $C_8H_{12}O_3N_2=184{\cdot}2$. No assay is described, but it has a m.p. of 189° to 192°. Barbital, *U.S.P.*, has a m.p. of 188° to 192°. Diemalum, *P.Dan.*, contains 98·3 to 100·4 per cent of barbitone, determined by Kjeldahl method; each ml. of N/10 hydrochloric acid is equivalent to 0·00921 g. of $C_8H_{12}O_3N_2$. An official method for the determination of barbitone is described in the A.O.A.C. 'Official Methods of Analysis', p. 590. The method is similar to that of the *U.S.P.* for Barbital Tablets (see under Tablets of Barbitone, p. 57) except that the preliminary extraction with ether is omitted and, to assist in removing the last traces of chloroform and to obtain a crystalline residue, the residue is repeatedly dissolved in 2 to 3 ml. of ether and the solvent removed. The purity of the residue is checked by determining its m.p.

National Library of Medicine: IGM Full Record Screen

TITLE:	**[Constituents of essential oil of imported myrrh and gum opoponax]**
AUTHOR:	**Tian J; Shi S**
AUTHOR AFFILIATION:	**National Institute for the Control of Pharmaceutical and Biological Products, Beijing.**
SOURCE:	**Chung Kuo Chung Yao Tsa Chih 1996 Apr;21(4):235-7, 256**
NLM CIT. ID:	**97352277**
ABSTRACT:	**The constitutents of essential oil in two kinds of Myrrha were analyzed by GC-MS. Fifteen compounds in Myrrh and thirty-three compounds in Gum opoponax were identified with their percent contents given. The main constituent of Myrrh is furanoeudesma-1,3-diene, and the main constituent of Gum opoponax is beta-trans-ocimene.**
MAIN MESH SUBJECTS:	**Drugs, Chinese Herbal/*CHEMISTRY/CLASSIFICATION Oils, Volatile/CHEMISTRY/*ISOLATION & PURIF**
ADDITIONAL MESH SUBJECTS:	**Comparative Study English Abstract Mass Fragmentography Support, Non-U.S. Gov't**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Chi**
REGISTRY NUMBERS:	**0 (Drugs, Chinese Herbal) 0 (Oils, Volatile)**

A. INGREDIENT NAME:

PHENINDAMINE TARTRATE

B. Chemical Name:

1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno-[2,1*c*]pyridine hydrogen tartrate.

C. Common Name:

Thephorin, Dalca, Nolamine, Melodan, Cerose, Carrhist

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Limits)	*(Results)*
Dry Basis:	98.0% - 101.5%	99.7%

E. Information about how the ingredient is supplied:

A white to cream white crystalline powder. Is odorless or almost odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

Arg., Br., Ind., Int., and Turk.
British Pharmacopeia 1993

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Witek, T. J., Canastrari, D. A., and Miller, R. D. The effects of phenindamine tartrate on sleepiness and psychomotor performance. *J. Allergy Clin Immunol,* 1992;90(6 Pt 1): 953-961.

Sigidinenko, L. V. Various principles of therapeutic tactics in epilepsy patients during pregnancy. *Zh Nevropatol Psikhiatr,* 1984; 84(6): 897-899.

H. Information about dosage forms used:

Tablets
Liquid
Elixir
Capsules

I. Information about strength:

25-50mg

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 162-167° with decomposition.
Solutions were unstable above pH 7 and were most stable at pH 3.5-5. Heating could cause phenindamine to isomerise to an inactive form.

L. Formulations:

M. Miscellaneous Information:

55-2779
30248

CERTIFICATE OF ANALYSIS

Product: PHENINDAMINE TARTRATE
Lot No.: 587-65-256
Date of Analysis: November 11, 1993

TESTS	LIMITS	RESULTS
Identification:		
A. Acetic Anhydride and Acetic Acid Test:	A red-violet color must be produced.	Passes Test.
B. Pyridine and Acetic Anhydride Test:	An emerald green color must be produced.	Passes Test.
C. Infrared Spectrum:	Agrees with reference standard.	Passes Test.
D. Ultraviolet:		
1. Specturm:	Maximum wavelength must be 260 ± 2 nm and minimum at 241 ± 2 nm.	Passes Test.
2. Absorptivities:	Abs. must not differ by more than 3.0%.	1.7%
pH:	3.0 to 4.0	3.5
Loss on Drying:	NMT 1.5%	0.11%
Residue on Ignition:	NMT 0.25%	0.007%
Heavy Metals:	NMT 0.002%	<0.002%
Iron:	NMT 0.005%	<0.005%
Isophenindamine:	NMT 2.0%	1.3%
Assay:		
A. As is Basis:	NLT 96.5%	99.6%
B. Dry Basis:	98.0% to 101.5%	99.7%

10/94

QUALITY CONTROL REPORT

CHEMICAL NAME.: PHENINDAMINE TARTRATE

MANUFACTURE LOT NO.:

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1)DESCRIPTION.:
A WHITE TO CREAM WHITE CRYSTALLINE POWDER.IS ODORLESS OR ALMOST ODORLESS.

2)SOLUBILITY.:
SOLUBLE IN 70 PARTS OF WATER;SLIGHTLY SOLUBLE IN ETHANOL (96%); PRACTICALLY INSOLUBLE IN CHLOROFORM AND IN ETHER.

3)MELTING POINT.:
MELTS AT ABOUT 162-167 degree WITH DECOMPOSITION.

4)SPECIFIC GRAVITY.:

5)IDENTIFICATION.:
A)COMPLIES (A) AS PER CO.SPECS.
B)COMPLIES (B) AS PER CO.SPECS.
C)COMPLIES (C) AS PER IR SPECTRUM CO.SPECS.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:ABOVE TEST IS CARRIED OUT BY SUPPLIER CERT.OF ANALYSIS.

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

ALFA CHEM

1661 N.SPUR DR. C.ISLIP, NY 11722-4325

TEL:(516) 277-7681
TLX: 650 481 1992
FAX:(516) 277-7681

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

IDENTIFICATION:

Product Name: Pheninda mine tartrate

CAS Registry Number: 569-59-5

RTECS Accession Number: NK9460700 Date of Issue: 3/3/92

Chemical Names: 1. 1H-indeno(2,1-c)pyridine,2,3,4,9-tetrahydro-2-methyl-9-phenyl-,tartrate.
2. 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1H-indeno(2,1-c)pyridine tartrate.

Synonyms: 1. Pheninda mine acid tartrate.
2. Pheninda mine tartrate.

SUMMARY:

Pheninda mine tartrate is an antihistamine which may have a stimulant effect. It is toxic if ingested in larger than therapeutic quantities. Wear a NIOSH-approved respirator, goggles, and gloves when handling the material. Use only with adequate ventilation. Wash exposed skin with soap and water. Sweep up spilled material for recovery and flush the swept spill area once with detergent and water. If the spilled material cannot be recovered, incineration is the recommended disposal procedure.

MATERIAL SAFETY DATA SHEET

HAZARDOUS INGREDIENTS:

Hazardous Components	CAS Number	Percent	OSHA PEL	ACGIH TLV
Phenindamine tartrate	569-59-5	not <98.5	n/a	n/a

PHYSICAL DATA:

Description/odor: White or almost white, almost odorless, voluminous powder.

Melting Range: 160 to 162 degrees C. Boiling Point: n/a

Vapor Density: n/a Vapor Pressure: n/a

Solubility: Soluble in 70 parts of water.

Molecular Weight: 411.45 Specific Gravity: n/a

Molecular Formula: C19H19NC4H6O6 Evaporation Rate:

FIRE AND EXPLOSION DATA:

Flash Point: n/a Flammable Limits: n/a

LEL: n/a UEL: n/a

Extinguishing Media: Water spray, carbon dioxide, or dry chemical.

Special Fire Fighting Instructions:

Isolate hazard and evacuate confined areas. Stay upwind, avoid smoke and fumes. Use water spray to wet containers. If smoke and fumes cannot be avoided, wear a chemical-proof suit with hood and breathing air supply. Fight fire from maximum distance.

Unusual Fire and Explosion Hazards: n/a

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

REACTIVITY DATA:

Stability: Stable.

Conditions to Avoid: n/a

Incompatibility: n/a

Hazardous Decomposition or Byproducts: When heated to decomposition, toxic fumes such as nitrogen oxides and carbon monoxide are emitted.

HEALTH DATA:

Toxicity (Reference 2):

Oral LD50	-	rat:	280 mg/kg.
Oral LD50	-	mouse:	255 mg/kg.
Oral LD50	-	rabbit:	577 mg/kg.
Intraperitoneal LD50	-	mouse:	68 mg/kg.
Intravenous LD50	-	mouse:	18 mg/kg.
Subcutaneous LDLo	-	rat:	200 mg/kg.

Saks: Highly toxic by oral administration.
OSHA: Toxic material.

Routes of Entry: Inhalation, ingestion, and dermal.

Acute or Chronic Health Hazards: n/a

Signs and Symptoms of Exposure:

ACUTE SKIN: Allergic reactions and skin sensitization may occur.

INGESTION: Small amounts ingested could lead to nausea, vomiting, diarrhea, anorexia, epigastric pain, blurred vision, tightness of the chest, muscular weakness, headaches, and CNS stimulation. Larger amounts could lead to coma and convulsions.

INHALATION: No information available.

CHRONIC EXPOSURE: Might impair the power of voluntary motion.

Medical Conditions Generally Aggravated by Exposure: Acute vesicular and exudative dermatosis, narrow angle glaucoma, hepatic or cardiovascular disorders, focal lesions of the cerebral cortex.

MATERIAL SAFETY DATA SHEET

Emergency and First Aid Procedures:

Product on Skin:	Immediately wash with water and soap. Remove contaminated clothing while washing proceeds. Contaminated clothing should be washed or dry-cleaned before reuse. Get medical attention if necessary.
Product Inhaled:	Remove from exposure, keep warm, and at rest. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Get medical attention if necessary.
Product Ingested:	If conscious, induce vomiting by giving ipecac syrup or two glasses of warm water followed by tickling the back of the throat with a tongue depressor. After vomiting stops, give the patient one or two tablespoons of activated charcoal in a glass of water. Get medical attention immediately.
Product in Eye:	Immediately flush the eyes with large amounts of water for 15 minutes. Lift upper and lower lids occasionally. Get medical attention if necessary.

Carcinogenicity: Not listed as a carcinogen by OSHA, ACGIH, NTP, or IARC.

Target Organs: None listed.

Safety Precautions: Avoid breathing the dust.
Avoid contact with eye and skin.
Wash thoroughly after handling.

PROTENTION INFORMATION:

Use with adequate ventilation to prevent dust build up. Wear a NIOSH-approved respirator, gloves, goggles, and other appropriate protective equipment to prevent exposure when handling the product.

MATERIAL SAFETY DATA SHEET

SPILL AND DISPOSAL INFORMATION:

Shovel large quantities of spilled material into drums. Sweep up the spill area and save the swept-up material for recovery. Wash the swept spill area once with detergent and water. If the material cannot be recovered, the preferred method of disposal is incineration in a facility which complies with all federal, state, and local requirements.

STANDARDS AND REGULATIONS:

DOT: Not regulated.

IATA: Not regulated.

IMO: Not regulated.

MATERIAL SAFETY DATA SHEET

REFERENCES:

1. Dangerous Properties of Industrial Materials, N. Irving Sax, Sixth Edition, Van Nostrand Reinhold Company, Inc., 135 West 50th Street, New York, NY 10020.

2. Registry of Toxic Effects of Chemical Substances Service, July 1991, update 9107.

3. NIOSH Pocket Guide To Chemical Hazards, U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health, Washington, D.C., June 1990.

4. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man , Geneva: World Health Organization, International Agency for Research on Cancer, 49 Sheridan Street, Albany, New York.

5. IATA Dangerous Goods Regulations, International Air Transport Association, Montreal, Quebec, Canada. 33rd Edition, 1992.

6. International Maritime Dangerous Goods Code, International Maritime Organization, London, England, 1982.

7. Code of Federal Regulations, Title 49, Parts 100 to 177, 1988.

8. Code of Federal Regulations, Title 29, Part 1910, Subpart Z, 1988.

9. Clinical Management of Poisoning and Drug Overdose, Haddad and Winchester, 1983, W.B. Saunders Co. Philadelphia.

10. Handbook of Emergency Toxicology, Sidney Kaye, Fifth Edition, 1988.

11. Martindale-The Extra Pharmacopoeia, 29th Edition, Edited by James E.F. Reynolds, 1989, Pharmaceutical Press, London, England.

12. American Hospital Formulary Service-Drug Information 88, American Society of Hospital Pharmacists, Bethesda, MD, 1989.

MATERIAL SAFETY DATA SHEET

Product: PHENINDAMINE TARTRATE

13. AMA Drug Evaluations, 5th, Edition, American Medical Association, W.B. Saunders Company, Philadelphia, PA, 1983.

14. The Merck Index, 10th Edition, Merck & Co., Inc., Rahway, NJ, 1983.

15. The Sigma-Aldrich Library of Chemical Safety Data, 1st. Edition, Edited by Robert E. Lenga, Sigma-Aldrich Corp., Milwaukee, WI, 1985.

16. Fourth Annual Report on Carcinogens, U.S. Dept. of Health and Human Services, Research Triangle Park, N.C., National Toxicology Program, 1985.

17. Handbook of Toxic and Hazardous Chemicals and Carcinogens, 3rd. Edition, Marshall Sittig, Princeton University (retired), 1991.

6148-y

Methdilazine *(U.S.P.)*. 10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine.
$C_{18}H_{20}N_2S = 296.4$.

CAS — 1982-37-2.

Pharmacopoeias. In *U.S.*

A light tan crystalline powder with a characteristic odour. M.p. 83° to 88° with a range of not more than 2°. Methdilazine 7.2 mg is the equivalent of approximately 8 mg of methdilazine hydrochloride. Practically **insoluble** in water; soluble 1 in 2 of alcohol, 1 in 1 of chloroform, and 1 in 8 of ether; freely soluble in 3M hydrochloric acid. **Store** in airtight containers. Protect from light.

Methdilazine has actions and uses similar to those of methdilazine hydrochloride. It is given in usual doses of 7.2 mg two to four times daily.

Preparations

Methdilazine Tablets *(U.S.P.)*. Tablets containing methdilazine. Store in airtight containers. Protect from light.

Proprietary Names
Tacaryl *(Westwood, USA)*.

6149-j

Methdilazine Hydrochloride *(U.S.P.)*. 10-(1-Methylpyrrolidin-3-ylmethyl)phenothiazine hydrochloride.
$C_{18}H_{20}N_2S,HCl = 332.9$.

CAS — 1229-35-2.

Pharmacopoeias. In *U.S.*

A light tan crystalline powder with a slight characteristic odour. It darkens on exposure to light. M.p. 184° to 190°. **Soluble** 1 in 2 of water and of alcohol, and 1 in 6 of chloroform; practically insoluble in ether; soluble in 0.1 M hydrochloric acid and 0.1 M sodium hydroxide solution. A 1% solution in water has a pH of 4.8 to 6. **Store** in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions. As for the antihistamines in general, p.1294.
As with all phenothiazine derivatives it should be used cautiously in patients with hepatic diseases.

Uses. Methdilazine hydrochloride is a phenothiazine derivative with the properties and uses of the antihistamines (see p.1295). It is more potent than promethazine and generally causes less sedation. It has a duration of action of 8 to 12 hours. It has serotonin-antagonising and anticholinergic properties.
Methdilazine hydrochloride is given for the symptomatic treatment of allergic conditions, particularly to control pruritus. It may also be given for pruritus of non-allergic origin. The usual dose is 8 mg twice daily and may be increased to 4 times daily if necessary. Children may be given 300 μg per kg body-weight daily in 2 divided doses.

Allergy. Ninety-six patients suffering from allergy, of whom 58% had pruritus and 27% hay fever, were studied over 2 weeks in a double-blind study designed to compare methdilazine hydrochloride with promethazine hydrochloride. The dose was usually 8 mg of the former and 20 mg of the latter, twice daily in syrup. Both drugs gave relief to about one-half the patients and there was little difference in efficacy for pruritus, but promethazine was superior to methdilazine in the relief of hay fever. Drowsiness occurred in 32% of the patients when they were taking promethazine, being twice the incidence seen with the other drug, but in spite of this the patients generally preferred it.—Report No. 25 of the General Practitioner Research Group, *Practitioner*, 1962, *188*, 803.

Migraine. Methdilazine 4 to 8 mg thrice daily was useful to prevent or reduce the frequency of migraine attacks.— J. M. Sutherland, *Drugs*, 1973, *5*, 212.

For a report of the use of methdilazine in the treatment of migraine, see Methysergide Maleate, p.669.

Preparations

Methdilazine Hydrochloride Syrup *(U.S.P.)*. A syrup containing methdilazine hydrochloride, with alcohol 6.5 to 7.5%. pH 3.3 to 4.1. Store in airtight containers. Protect from light.

Methdilazine Hydrochloride Tablets *(U.S.P.)*. Tablets containing methdilazine hydrochloride. Store in airtight containers. Protect from light.

Proprietary Names
Dilosyn *(Allen & Hanburys, Austral.; Allen & Hanburys, Canad.)*; Tacaryl *(Mead Johnson, Austral.; Pharmacia, Swed.; Westwood, USA)*; Tacryl *(Pharmacia, Denm.)*.

Methdilazine hydrochloride was formerly marketed in Great Britain under the proprietary name Dilosyn *(Duncan, Flockhart)*.

6150-q

Metiamide. SKF 92058. 1-Methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]thiourea.
$C_9H_{16}N_4S_2 = 244.4$.

CAS — 34839-70-8.

Adverse Effects. Metiamide may cause agranulocytosis.

Acute reversible neutropenia occurred in 2 patients given metiamide.— J. A. H. Forrest *et al.* (letter), *Lancet*, 1975, *1*, 392. Bone-marrow depression due to metiamide was thought to be due to the thiourea present in the metiamide molecule, rather than to H_2-receptor blockade.— *ibid.*, 1975, *2*, 802.

A further 4 cases of metiamide-induced agranulocytosis had occurred and trials had stopped.— W. L. Burland, *et al.*, *Smith Kline & French* (letter), *Lancet*, 1975, *2*, 1085.

Further references: E. J. Feldman and J. I. Isenberg, *New Engl. J. Med.*, 1976, *295*, 1178.

Uses. Metiamide is a histamine H_2-receptor antagonist (see p.1294) with actions similar to those of cimetidine (p.1303) but a shorter duration of action. It has been used in doses of 1 g daily in conditions associated with gastric hyperacidity but has been found to cause bone-marrow depression.

References to the action and uses of metiamide: R. W. Brimblecombe *et al.*, *S. Afr. med. J.*, 1974, *48*, 2253; D. M. Shepherd *et al.*, *Digestion*, 1974, *11*, 307; B. Thjodleifsson and K. G. Wormsley, *Br. med. J.*, 1974, *2*, 304; *idem*, *Gut*, 1975, *16*, 501; G. I. Barbezat *et al.*, *Gut*, 1975, *16*, 186; J. I. Isenberg, *Ann. intern. Med.*, 1976, *84*, 212; A. S. MacDonald *et al.* (preliminary communication), *Lancet*, 1976, *1*, 68; J. M. Hind and T. J. Sutton, *J. Pharm. Pharmac.*, 1977, *29*, 244; O. R. Griffith *et al.*, *Br. J. Pharmac.*, 1978, *64*, 416P.

Duodenal ulcers. References to the use of metiamide in duodenal ulcers: M. Mainardi *et al.*, *New Engl. J. Med.*, 1974, *291*, 373; G. J. Milton-Thompson *et al.*, *Lancet*, 1974, *1*, 693; R. E. Pounder *et al.*, *Br. med. J.*, 1975, *2*, 307; *Lancet*, 1975, *2*, 779; *ibid.*, 802; R. Earlam (letter), *ibid.*, 973; J. H. B. Saunders and K. G. Wormsley, *Lancet*, 1977, *1*, 765.

Zollinger-Ellison syndrome. References to the use of metiamide in the Zollinger-Ellison syndrome: M. H. Thompson *et al.* (letter), *Lancet*, 1975, *1*, 35; L. G. Halloran *et al.* (letter), *ibid.*, 281; E. R. Smith *et al.*, *Med. J. Aust.*, 1976, *1*, 1000; D. M. McCarthy *et al.*, *Ann. intern. Med.*, 1978, *87*, 668; J. K. Siepler *et al.*, *Am. J. Hosp. Pharm.*, 1978, *35*, 141.

Manufacturers
Smith Kline & French, UK.

6151-p

Oxomemazine. RP 6847; Trimeprazine *SS*-Dioxide. 10-(3-Dimethylamino-2-methylpropyl)phenothiazine 5,5-dioxide.
$C_{18}H_{22}N_2O_2S = 330.4$.

CAS — 3689-50-7.

A white crystalline powder with a bitter taste. M.p. 155°. Practically **insoluble** in water; slightly soluble in alcohol; soluble in chloroform and ether.

6152-s

Oxomemazine Hydrochloride.
$C_{18}H_{22}N_2O_2S,HCl = 366.9$.

CAS — 4784-40-1.

Crystals. M.p. 250°. Oxomemazine hydrochloride 11.1 mg is approximately equivalent to 10 mg of oxomemazine.

Oxomemazine is a phenothiazine derviative with the properties and uses of the antihistamines (see p.1294). It has been given both as the base and as the hydrochloride in doses equivalent to 10 to 40 mg of oxomemazine daily.

Proprietary Names
Doxergan *(Specia, Belg.; Specia, Fr.; Specia, Neth.; Specia, Switz.)*; Imakol *(Rhône-Poulenc, Ger.)*.

6153-w

Phenindamine Tartrate *(B.P.)*. Phenindamine Tartras; Phenindaminium Tartrate; Phenindamine Acid Tartrate. 1,2,3,4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene hydrogen tartrate; 2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrogen tartrate.
$C_{19}H_{19}N,C_4H_6O_6 = 411.5$.

CAS — 82-88-2 (phenindamine); 569-59-5 (tartrate).

Pharmacopoeias. In *Arg.*, *Br.*, *Ind.*; *Int.*, and *Turk.*

A white or almost white, almost odourless, voluminous powder with a bitter taste. M.p. 160° to 162°; on further heating it solidifies and melts again at about 168° with decomposition. **Soluble** 1 in 70 of water and 1 in 300 of alcohol; practically insoluble in chloroform and ether. A 1% solution in water has a pH of 3.4 to 3.9. **Store** in airtight containers. Protect from light.

Incompatibility. Incompatible with alkalis, sodium salicylate, phosphates, and oxidising substances. Solutions were unstable above pH 7 and were most stable at pH 3.5 to 5. Heating could cause phenindamine to isomerise to an inactive form.— *J. Am. pharm. Ass. (Pract. Pharm. Edn)*, 1956, *17*, 273.

Adverse Effects, Treatment, and Precautions. As for the antihistamines in general, p.1294. Unlike most other antihistamines phenindamine tartrate may have a stimulant effect; to avoid the possibility of insomnia it should not be given after 4 p.m.

Allergy. In a modified 'repeated-insult' patch test, phenindamine tartrate was found to produce extreme sensitisation of the skin.— A. M. Kligman, *Universal Derm.*, 1966, *47*, 393.

Extrapyramidal symptoms. For a report of tardive dyskinesia associated with the use of phenindamine, see Brompheniramine Maleate, p.1298.

Uses. Phenindamine tartrate has the properties and uses of the antihistamines (see p.1295). It is less potent than promethazine but it does not generally produce drowsiness and may even be mildly stimulating. It has a moderate anticholinergic action.
Phenindamine tartrate is given in doses of 25 to 50 mg up to thrice daily.

Preparations

Phenindamine Tablets *(B.P.)*. Tablets containing phenindamine tartrate. They are sugar-coated.

Thephorin *(Sinclair, UK)*. Phenindamine tartrate available as tablets of 25 mg. (Also available as Thephorin in *Austral.*, *S.Afr.*).

ʏCLIDINE HYDROCHLORIDE

phenylthiocarbamate.
basmolytic agent.
'CLIDINE HYDROCHLORIDE. (Parke,
1-(1-phenylcyclohexyl)piperidine hydro-
:.
ernyl
nalgesic, anesthetic.
ETRAZINE BITARTRATE. Calorie
0.3/Tab. See: Plegine (Ayerst Lab.)
RINE. (MacAllister) Amphetamine sulfate.
oz., 1 pt., 1 gal.
entral nervous system stimulant.
I GERMICIDAL SOLUTION & TINC-
(Ulmer) Benzalkonium Chloride,
1%. Bot. 1 qt. & 1 gal.
.ZINE SULFATE, N.N.D. 1963. Mono-
xidase inhibitor, beta-phenylethyl-
ne sulfate. See: Nardil (Warner-Chilcott)
GAN HCl, N.N.D. 1963. (Wyeth)
thazine) N-(2'-Dimethylamino-2'-
ethyl)phenothiazine HCl.
2%, Tube 1.12 oz. Lot., Phenergan 2%,
mine 15%. Bot. 4 oz.
25 mg.) Box 12s.
ntihistaminic.
GAN EXPECTORANT TROCHES.
Ph 1.5 mg., ipecac pow. ext. 2.3
ot. sulfonate 162 mg./Troche.
.
Expectorant.
GAN EXPECTORANT TROCHES W/
NE. (Wyeth) Phenergan 1.5 mg., codeine
., ipecac pow. ext. 2.3 mg., Pot.
l sulfonate 162 mg./Troche. Jar 36s.
Expectorant.
GAN HYDROCHLORIDE, N.N.D. 1960.
. **Expectorant:** Phenergan HCl 5 mg.,
ephrine HCl 5 mg., ipecac fldxt. 0.17
ot. guaiacol sulfonate 44 mg., chloro-
25 mg., *citric acid* 60 mg., *Sod. citrate*
./5 cc. Bot. 1 pt. Also avail. w/codeine
ate 1/6 gr./dr. Supp. 25 mg. Box 12s.
Phenergan HCl 6.25 mg./5 cc. Also
25 mg./5 cc. Bot. 1 pt. **Tab.:** Phenergan
.5 mg. & 50 mg./Tab. Bot. 100s.
GAN INJECTION. (Wyeth) Promethazine
Vial (25 mg./cc.) 10 cc.; (50 mg./cc.) 10

.M., I.V., antihistaminic.
GAN PEDIATRIC. (Wyeth) Dextro-
phan HBr 7.5 mg., promethazine HCl 5.0
uidextract ipecac 0.17 min., pot.
lsulfonate 44 mg., min. chloroform 0.25
tric acid 60 mg., sod. citrate 197 mg./5
t. pt.
ntitussive.

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name recognized as USAN or by N.F.,
r N.N.D.

***PHENERIDINE.** 1-(b-phenyl-b-ethyl)-4-carbethoxy-4-phenylpiperidine.
***PHENETHICILLIN POTASSIUM,** N.N.D. 1963. Alpha-phenoxyethyl penicillin pot. Penicillin-152 *pot. See: Alpen, Tabs. (Schering)*
Broxil (Beecham Res.)
Chemipen, Tab. (Squibb)
Darcil (Wyeth)
Dramcillin-s (White)
Maxipen, Tab. (Roering)
Ro-Cillin, Tabs. (Rowell)
Semopen, Tab., Pow. (Massengill)
Syncillin, Tab. (Bristol)
PHENETRON INJECTABLE. (Lannett) Chlorpheniramine maleate 100 mg./cc. Vial 5 cc.
PHENETSAL, N.N.R. 1948.
See: Salophen, Tab. (Winthrop Labs.)
***PHENFORMIN HCl,** N.N.D. 1963. N¹-phenethylbiguanide HCl.
See: D.B.I. (U.S. Vitamin)
PHENICHTHOL. (Parke, Davis) Phenol 2%, ammonium ichthosulfonate, alum & lead plaster.
Use: Antiseptic.
***PHENINDAMINE TARTRATE,** U.S.P.; Syr. or Tab., U.S.P. 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene tartrate.
See: Thephoria, Prep. (Roche)
W/Aluminum aspirin, chlorpheniramine maleate, phenylephrine HCl.
See: Dalca, Tabs. (Ascher)
W/Chlorprophenpyridamine maleate, phenylpropanolamine HCl.
See: Nolamine, Tab. & Elix. (G.W. Carnrick)
W/Dextromethorphan, chlorpheniramine, maleate, phenylephrine HCl, menthol.
See: Melodan, Syp. (Mayrand)
W/Dextromethorphan HBr, phenylephrine.
See: Cerose, Pediatric (Ives-Cameron)
W/Phenylephrine hydrochloride, caramiphen *ethanedisulfonate. See: Dondril (Whitehall Labs.)*
W/Phenylephrine HCl, chloroform, ipecac fldxt., glycerin, pot. guaiacol sulfonate, sod. citrate, citric acid. See: Cerose, Liq. (Ives-Cameron)
W/Pyrilamine maleate, chlorpheniramine maleate, phenylephrine. See: Carrhist Elixir (Carrtone)
W/Sulfadimethoxine, N-acetyl-p-aminophenol, caffeine. See: Madricidin, Cap. (Roche)
***PHENINDIONE,** N.N.D. 1963. (2-Phenylindane-1,3-Dione; 2-Phenyl-1,3-Indandione; Phenylindanedion, Dindevan)
See: Danilone, Tab. (Schieffelin)
Hedulin, Tab. (Walker)
Indon, Tab. (Parke, Davis)
PHENIODOL. See: Iodoalphionic Acid
***PHENIPRAZINE HCl.**
See: Catron, Tab. (Lakeside)
***PHENIRAMINE.** 1-Phenyl-1-(2-pyridyl)-3-dimethylaminopropane. (No pharmaceutical form available.)

W/*Codeine phosphate.*
See: Antosen, Syr. (Squibb)
W/Scopolamine HBr.
See: Nio-Piracene, Tab. (Nion)
***PHENIRAMINE MALEATE,** N.F., N.N.D. 1963 Tab., N.F.; Ophth. Sol., N.F. 1-Phenyl-1-(2-pyridyl)-3-dimethylamino-propane maleate. Prophenpyridamine.
See: Inhiston (Upjohn)
Trimeton (Schering)
W/Acetophenetidin, aspirin, phenobarbital, hyoscyamine sulfate, phenylephrine HCl.
See: Phenaphen Plus, Tab. (Robins)
W/*Ammonium chloride, Sod. citrate & chloroform.*
See: Trimetosa, Syr. (Schering)
W/d-Amphetamine sulfate, chloroform, menthol & alcohol.
See: Tussate, Syr. (Pitman-Moore)
W/Dihydrocodeinone bitartrate, Pot. guaiacol sulfonate, Sod. citrate, citric acid & chloroform.
See: Tussar, Liq. (Armour)
W/Dihydrocodeinone bitrartrate, Vit. C, pyrilamine maleate *pot. citrate.*
See: Citra Forte. (Boyle)
W/Dihydrocodeinone bitratrate, phenylpropanolamine HCl, pyrilamine maleate, glyceryl guaiacolate, chloroform.
See: Tussaminic Expectorant, Syp. (Smith-Dorsey)
W/Dihydrocodeinone bitartrate, pyrilamine maleate, phenylephrine HCl, pot. guaiacol-sulfonate, cherry flavor.
See: Nova-Tussa, Liq. (Drug Specialties-Prane)
W/Doxylamine succinate, pyrilamine maleate.
See: Tridecamine, Tab. (National)
W/*Ephedrine sulfate & ammonium chloride.*
See: Extosen, Syr. (Squibb)
W/Glyceryl guaiacolate, desoxyephedrine HCl & codeine phosphate.
See: Robitussin A-C, Syr. (Robins)
W/Hesperidin, ascorbic acid, thenylpyramine fumarate, pyrilamine maleate, salicylamide, caffeine. See: Tripac, Cap. (Person & Covey)
W/Hesperidin, phenylephrine HCl, methapyrilene HCl, pyrilamine maleate, vit. C, salicylamide, acetophentidin, caffeine.
See: Boyle Citra, Caps. (Boyle)
W/Narcotine, phenylephrine HCl, chloroform, menthol. *See: Conar, Liq. (Massengill)*
W/Phenylephrine HCl.
See: Isohist, Ophth. Sol. (Broemmel)
W/Phenylephrine HCl.
See: Phenistan, Tab. (Chicago Pharm.)
W/Phenylephrine HCl, acetyl-p-aminophenol, atropine sulfate.
See: TPC, Tab. (Tennessee Pharm.)
W/Phenylephrine HCl, methapyrilene HCl, pyrilamine maleate, aspirin, acetophenetidin, caffeine, Vit. C, hesperidin.
See: Darbacin, Cap. (Crestmed)
W/Phenylephrine HCl, pyrilamine
ascorbic acid. See: Corizahist,
W/Phenylephrine HCl, pyrilamine
methapyrilene HCl.
See: Citra H.F., Cap. (Boyle)
W/Phenylephrine HCl & A.P.C.
W/A.P.C., Cap. (Pitman-Moore)
See: Novahistine
W/*Phenylephrine HCl, chloroform*
See: Novahistine, Elixir. (Pitm
W/Phenylpropanolamine HCl, glyc
See: Darathon, Sol. (Grail)
W/Phenylpropanolamine HCl, pyril
See: Triaminic, Preps. (Smith-D
W/Phenylpropanolamine HCl, phen
pyrilamine maleate.
See: Synergen, Elix. (Lemmon)
W/Phenylpropanolamine HCl, phen
pyrilamine maleate, acetyl-p-ami
See: Phenagesic (Dalin)
W/Pyrilamine maleate.
See: Triaminic, Tab. (Smith-Do
W/Pyrilamine maleate, dioxylamin
See: Tridecamine, Tab. (Merrel
W/Pyrilamine maleate & methapyri
See: Incorpohist, Tab. (Blue L
Pediahist, Syr. (Columbus)
Pyma Timed, Cap. (Testagar)
W/Pyrilamine maleate, phenylprop
See: Trialler, Tab. (Lemor)
W/Pyrilamine Maleate, phenylprop
trisulfapyrimidines.
See: Trisulfaminic, Prep. (Smit
W/Pyrilamine Maleate & phenyltol
dihydrogen citrate.
See: Multihist, Cap. & Syr. (Sm
W/Salicylamide, acetophenetidin,
ascorbic acid, hesperidin purifie
See: Coryban, Cap. (Roerig)
W/Scopolamine hydrobromide, alum
gel, ethyl aminobenzoate.
See: Daptren, Tab. (Davis & S
W/Thenylpyramine HCl, pyrilamine
phenylpropanolamine.
See: Histene, Tab. (Paul Mane
W/Tyrothricin, neomycin, benzoc
See: Neo-T-Cain, Lozenges (C
W/*Vit. C, aspirin & alkalizing ba*
See: Cehistra, Tab. (Organon)
PHENIRATAN. (Irwin, Neisler)
tannate 15 mg./Tab. Bot. 100s
Use: Antihistamine.
***PHENISOHONE HBr.** 3, 4-dihy
isopropylaminopropiophenone H
See: Dapanone HBr (Merck, Sha
PHENISTAN. (Chicago Pharm.)
10 mg., prophenpyridamine mal
tab. Bot. 50s, 100s, 1000s.

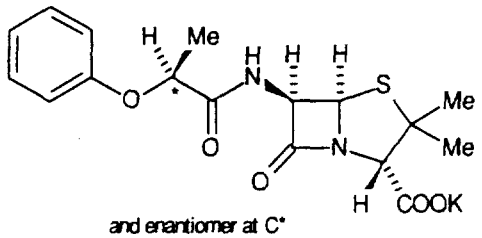
end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of iodine required. Each ml of 0.05M *iodine VS* is equivalent to 5.857 mg of $C_8H_{12}N_2,H_2SO_4$.

Storage Phenelzine Sulphate should be kept in a well-closed container and protected from light.

Preparation
Phenelzine Tablets

Action and use Monoamine oxidase inhibitor.

Phenethicillin Potassium



and enantiomer at C*

$C_{17}H_{19}KN_2O_5S$ 402.5 *132-93-4*

Definition Phenethicillin Potassium is potassium (6*RS*)-[(2*S*)-2-phenoxypropionamido]penicillanate. It contains not less than 97.0% and not more than 100.5% of $C_{17}H_{19}KN_2O_5S$, calculated with reference to the anhydrous substance.

Characteristics A white or almost white powder.

Freely soluble in *water*; sparingly soluble in *ethanol (96%)*; slightly soluble in *absolute ethanol* and in *chloroform*; practically insoluble in *ether*.

Identification A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of phenethicillin potassium.

B. Dissolve 10 mg in 10 ml of *water* and add 0.5 ml of *neutral red solution*. Add sufficient 0.01M *sodium hydroxide* to produce a permanent orange colour and then add 1.0 ml of *penicillinase solution*. The colour changes rapidly to red.

C. Heat 0.5 g with 10 ml of 5M *hydrochloric acid* under a reflux condenser for 4 hours, cool, add a mixture of 7 ml of 5M *sodium hydroxide* and 7 ml of *water* and extract with successive 10-ml quantities of *ether* until complete extraction is effected. Wash the combined ether extracts with *water*, filter through *anhydrous sodium sulphate* and evaporate the filtrate to dryness. The *melting point* of the residue, after recrystallisation from *petroleum spirit (boiling range, 40° to 60°)*, is about 116°, Appendix V A.

D. Ignite. The residue yields the reactions characteristic of *potassium salts*, Appendix VI.

Acidity or alkalinity pH of a 10% w/v solution, 5.5 to 7.5, Appendix V L.

Specific optical rotation In a 1% w/v solution in a solution containing 0.2% w/v of *dipotassium hydrogen orthophosphate* and 0.8% w/v of *potassium dihydrogen orthophosphate*, +217° to +244°, calculated with reference to the anhydrous substance, Appendix V F.

Iodine-absorbing substances Not more than 3%, calculated with reference to the anhydrous substance, when determined by the following method. Dissolve [illegible] g in sufficient water to produce 25 ml. To 10 ml add 10 ml of *mixed phosphate buffer pH 4.0* and 10 ml of 0.01M *iodine VS* and titrate immediately with 0.01M *sodium thiosulphate VS* using *starch mucilage*, added towards the end of the titration, as indicator. Repeat the operation without the substance being examined. The difference between the titrations represents the amount of iodine-absorbing substances present. Each ml of 0.01M *sodium thiosulphate VS* is equivalent to 0.425 mg of iodine-absorbing substances.

Water Not more than 1.5% w/w, Appendix IX C. Use 1.5 g.

Assay Dissolve 0.25 g in sufficient *water* to produce 500 ml and dilute 10 ml to 100 ml with *water*. Place two 2-ml aliquots of the resulting solution in separate stoppered tubes. To one tube add 10 ml of *imidazole—mercury reagent*, mix, stopper the tube and immerse in a water bath at 60° for exactly 25 minutes, swirling occasionally. Remove from the water bath and cool rapidly to 20° (solution A). To the second tube add 10 ml of *water* and mix (solution B). Without delay measure the *absorbances* of solutions A and B at the maximum at 325 nm, Appendix II B, using in the reference cell a mixture of 2 ml of *water* and 10 ml of *imidazole—mercury reagent* for solution A and *water* for solution B. Calculate the content of $C_{17}H_{19}KN_2O_5S$ from the difference between the absorbances of solutions A and B, from the difference obtained by repeating the operation using *phenethicillin potassium BPCRS* in place of the substance being examined and from the declared content of $C_{17}H_{19}KN_2O_5S$ in *phenethicillin potassium BPCRS*.

Storage Phenethicillin Potassium should be kept in a well-closed container.

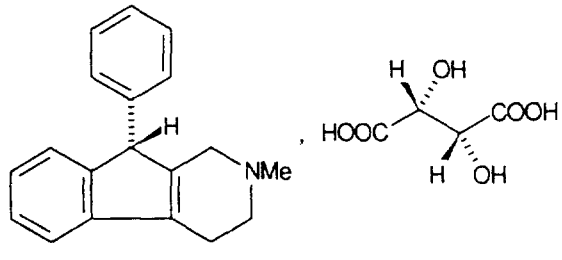
Labelling The label states (1) the date after which the material is not intended to be used; (2) the conditions under which it should be stored.

Preparations
Phenethicillin Capsules
Phenethicillin Tablets

1993 BP

Action and use Antibacterial.

Phenindamine Tartrate



and enantiomer

$C_{19}H_{19}N,C_4H_6O_6$ 411.5 *569-59-5*

Definition Phenindamine Tartrate is (*RS*)-2,3,4,9-tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrogen (2*R*,3*R*)-tartrate. It contains not less than 98.5% and not more than 101.0% of $C_{19}H_{19}N,C_4H_6O_6$,

MAIN MESH SUBJECTS: Histamine H1 Antagonists/*PHARMACOLOGY
Psychomotor Performance/*DRUG EFFECTS

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National Library of Medicine: IGM Full Record Screen

TITLE: The effects of phenindamine tartrate on sleepiness and psychomotor performance.

AUTHOR: Witek TJ Jr; Canestrari DA; Miller RD; Yang JY; Riker DK

AUTHOR AFFILIATION: Regulatory and Clinical Development, Richardson-Vicks USA (A Procter & Gamble Company), Shelton, Conn.

SOURCE: J Allergy Clin Immunol 1992 Dec;90(6 Pt 1):953-61

NLM CIT. ID: 93094481

ABSTRACT: Phenindamine, an H1-receptor antagonist that was developed almost 50 years ago, has been associated with both drowsiness and insomnia. Since its central nervous system profile has not been well characterized, we used a series of psychomotor tests to conduct two studies. In the first, 12 subjects received single oral doses of phenindamine (25 mg), diphenhydramine (50 mg), terfenadine (60 mg), or placebo in a four-way crossover study. Psychomotor tests included choice reaction time (CRT), tracking, and hand steadiness (HS). In the second trial, 15 subjects received single oral doses of phenindamine (25 mg), pseudoephedrine (60 mg), phenindamine and pseudoephedrine, diphenhydramine (50 mg), or placebo in a five-way crossover study. Psychomotor tests included CRT, HS, and a task that divided attention between tracking and reaction time. Introspective drowsiness was measured in both trials with use of a visual analog scale (VAS) and the Stanford Sleepiness Scale (SSS). All assessments were made before and 1, 3, and 5 hours after drug administration. In the first trial, diphenhydramine produced significant impairment relative to placebo ($p < 0.05$) in CRT, tracking, and HS tasks and higher SSS and VAS scores, with peak effect noted at 3 hours. Phenindamine did not significantly differ from placebo or terfenadine. In the second trial, diphenhydramine produced significant impairment relative to placebo ($p < 0.05$) in CRT, divided attention, HS, and VAS, and SSS, also peaking at 3 hours. Stanford Sleepiness Scale scores after phenindamine were greater than placebo at 3 hours ($p < 0.05$) but significantly less than diphenhydramine ($p < 0.05$).(ABSTRACT TRUNCATED AT 250 WORDS)

MAIN MESH SUBJECTS:	**Histamine H1 Antagonists/*PHARMACOLOGY** **Psychomotor Performance/*DRUG EFFECTS** **Pyridines/*PHARMACOLOGY** **Sleep/*DRUG EFFECTS**
ADDITIONAL MESH SUBJECTS:	**Adolescence** **Adult** **Diphenhydramine/PHARMACOLOGY** **Ephedrine/PHARMACOLOGY** **Human** **Middle Age** **Time Factors**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Histamine H1 Antagonists)** **0 (Pyridines)** **299-42-3 (Ephedrine)** **58-73-1 (Diphenhydramine)** **82-88-2 (phenindamine)**

☑

TITLE:	**[Various principles of therapeutic tactics in epilepsy patients during pregnancy]**
AUTHOR:	**Sigidinenko LV**
SOURCE:	**Zh Nevropatol Psikhiatr 1984;84(6):897-9**
NLM CIT. ID:	**84276611**
ABSTRACT:	**Forty-two epileptics were examined during pregnancy. According to the severity of the paroxysmal symptomatology, the authors identified three clinical groups: the first included patients with a therapeutic remission; the second, those with non-convulsive paroxysms; and the third group comprised patients with convulsive paroxysms. With due regard for impairments identified in the blood content of neurotransmitters, the patients received the multiple modality treatment, which included vitamins of group "B", potassium orotate, antihistamine drugs, the substitution of chloracon for phenobarbital and benzonal for diphenylhydantoin sodium; at the later stage of pregnancy the patients were given phenindamine tartrate. The use of the multiple modality treatment facilitated the cessation of attacks and served as the prevention of epileptic exacerbation in patients during the gestational and post-partal periods.**
MAIN MESH SUBJECTS:	**Anticonvulsants/*ADMINISTRATION & DOSAGE** **Epilepsy/BLOOD/*DRUG THERAPY** **Neurotransmitters/*BLOOD** **Pregnancy Complications/BLOOD/*DRUG THERAPY**
ADDITIONAL MESH SUBJECTS:	**Adult** **Drug Therapy, Combination** **English Abstract** **Epinephrine/BLOOD** **Female** **Histamine/BLOOD** **Human** **Norepinephrine/BLOOD** **Pregnancy** **Serotonin/BLOOD**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Rus**
REGISTRY NUMBERS:	**0 (Anticonvulsants)** **0 (Neurotransmitters)** **50-67-9 (Serotonin)** **51-41-2 (Norepinephrine)** **51-43-4 (Epinephrine)** **51-45-6 (Histamine)**

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TITLE:	**The structure of phenindamine base and salts in the solute state.**
AUTHOR:	**Branch SK; Casy AF; Hussain R; Upton C**
AUTHOR AFFILIATION:	**School of Pharmacy and Pharmacology, University of Bath, Bath, UK.**
SOURCE:	**J Pharm Pharmacol 1988 Jan;40(1):83-4**
NLM CIT. ID:	**88214661**
ABSTRACT:	**High-field NMR (13C and 1H) studies of phenindamine are reported which establish structures of the free base and some of its salts in the solute condition. The base exists as a mixture of two isomers which differ in double bond position (9-9a or 4a-9a) while most salts are 9-9a isomers. The clinically employed tartrate (Thephorin) is exceptional in being a 4a-9a ene. Salts of both double bond type exist in solution as mixtures of protonated epimers of variable epimeric ratio, that of the tartrate in D2O being approximately 1:1.**
MAIN MESH SUBJECTS:	**Pyridines/*ANALYSIS**
ADDITIONAL MESH SUBJECTS:	**Chemistry Crystallization Nuclear Magnetic Resonance Spectrophotometry, Ultraviolet**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Pyridines) 82-88-2 (phenindamine)**

A. INGREDIENT NAME:

PIRACETAM

B. Chemical Name:

1-Acetamido-2-Pyrrolidinone, Euvicor, Gabacet, Genogris, 2-Ketopyrrolidine-1-Ylacetamide, Nootron, Nootropil, Nootropyl, Normabrain, 2-Oxo-Pyrrolidine-Acetamide, 2-Oxo-Pyrrolidin-1-Ylacetamide, Piracetam, Pirazetam, Pirroxil, Pyracetam, Pyramem, 2-Pyrrolidininnoneacetamide, 2-Pyrrolidoneacetamide, UCB 6215

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.27%

E. Information about how the ingredient is supplied:

White or almost white crystal powder

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Mondadori, C. Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine. *Critical Reviews™ in Neurobiology,* 1996; 10: 357-370.

Tallal, U., Chase, C., and Russell, G. Calculation of the Efficacy of Piracetam in Treating Information Processing, Reading, and Writing Disorders in Dyslexic Children. *International Journal pf Psychophysiology,* 1986; 4: 41-52.

Mindus, P., Cronholm, B., and Levander, S. E. Piracetam-induced improvement of mental performance: a controlled study on normally aging individuals. *Acta Psychiat. Scand.*, 1976; 54(2):150-160.

Simeon, J., Waters, B., and Resnick, M. Effects of Piracetam in children with learning disorders. *Psychopharmacol.Bull.*, 1980; 16: 65-66.

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Wilsher, C., Atkins, G., and Mansfield, P. Piracetam as an aid to learning in dyslexia, preliminary report. *Psychopharmacology.* 1979; 65: 107-109.

Wilsher, C., Atkins, G., and Mansfield, P. Effects of Piracetam on dyslexic' reading ability. *J. Learn. Disability.* 1985; 18: 19-25.

Mondadori, C., Petschke, F., and Häusler, A. The Effects of Nootropics on Memory: new Aspects for Basic Research. *Pharmacopsychiatry.* 1989; 22: 102-106.

YaI, V., Derzhiruk, L. P., and Mogilevskii, A. Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents. *Neurosci Behav. Physiol.*, 1996; 26(6): 507-515.

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Pilch, H. and Muller, W. E. Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice. *Psychopharmacology.* 1988; 94(1): 74-78.

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Di Ianni, M., Wilsher, C. R., and Blank, M. S. The effects of Piracetam in children with dyslexia. *J. Clin Psychopharmacol.* 1985; 5(5): 272-278.

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Reisberg, B., Ferris, S. H., and Gershon, S. An overview of pharmacologic treatment of cognitive decline in the aged. *Am J. Psychiatry.* 1981; 138(5): 593-600.

Bartus, R. T., Dean, R. L., and Sherman, K. A. Profound effects of combining choline and Piracetam on memory enhancement and cholinergic function in aged rats. *Neurobiol Aging.* 1981; 2(2): 105-111.

Buresova, O. and Bures, J. Piracetam-induced facilitation of interhemispheric transfer of visual information in rats. *Psychopharmacologia.* 1976; 46(1): 93-102.

Dimond, S. J., Scammell, R. E., and Pryce, I. G. Some effects of Piracetam (UCB 6215, Nootropyl) on chronic schizophrenia. *Psychopharmacology.* 1979; 64(3): 341-348.

Dimond, S. J. and Brouwers, E. M. Increase in the power of human memory in normal man through the use of drugs. *Psychopharmacology.* 1976; 49(3): 307-309.

Sara, S. J., David-Remacle, M., and Weyers, M. Piracetam facilities retrieval but does not impair extinction of bar-pressing in rats. *Psychopharmacology.* 1979; 61(1): 71-75.

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Mondadoori, C., Classen. W., and Borkowski, J. Effects of oxiracetam on learning memory in animals: comparison with piracetam. *Clin Neuropharmacol.* 1986; 9 Suppl 3 S27-38.

Song, C., Earley, B., and Leonard, B. E. Effect of chronic treatment with piracetam and tacrine on some changes caused by thymectomy in the rat brain. *Pharmacol Biochem. Behav.* 1997; 56(4): 697-704.

H. Information about dosage forms used:

Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml. administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed. The patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

I. Information about strength:

1.65 g -3.3 g

J. Information about route of administration:

Orally

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

See File

CERTIFICATE OF ANALYSIS

30-3213
54051

Coa No: 7777

PIRACETAM

Batch No: 96120006

Manufacturing Date: Dec 3, 1996

Testing Result

Appearance	White or almost white crystal powder
Identification	Positive
Melting Point	152.5-153.5°C
Clarity of Solution	Clear
Heavy Metals	<20ppm
Residue on Ignition	0.02%
Loss on Drying	0.12%
Assay	99.27%

Conclusion: Conforms to China Provincial Standard

Remarks: The above testing result is per manufacturer's information.

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: PIRACETAM

MANUFACTURE LOT NO.: 97060036

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.___.

1) DESCRIPTION.:
WHITE TO OFF WHITE CRYSTALS FROM ISOPROPANOL OR WHITE TO OFF WHITE CRYSTALLINE POWDER.

2) SOLUBILITY.:
VERY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL, ESPECIALLY IN ISOPROPANOL.

3) MELTING POINT.:
MELTS AT ABOUT 151.5-152.5 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

---------- IDENTIFICATION ----------

PRODUCT #: P5295 NAME: PIRACETAM

CAS #: 7491-74-9

MF: C6H10N2O2

SYNONYMS

1-ACETAMIDO-2-PYRROLIDINONE * EUVIFOR * GABACET * GENOGRIS * 2-KETOPYRROLIDINE-1-YLACETAMIDE * NOOTRON * NOOTROPIL * NOOTROPYL *

NORMABRAIN * 2-OXO-PYRROLIDINE ACETAMIDE * 2-OXO-PYRROLIDIN-1-YLACETAMIDE * PIRACETAM * PIRAZETAM * PIRROXIL * PYRACETAM * PYRAMEM *

2-PYRROLIDINONEACETAMIDE * 2-PYRROLIDONEACETAMIDE * UCB 6215 *

---------- TOXICITY HAZARDS ----------

RTECS NO: UX9660500

1-PYRROLIDINEACETAMIDE, 2-OXO-

TOXICITY DATA

IPR-MUS LD50:>10 GM/KG	PCJOAU 23,795,89
SCU-MUS LD50:12 GM/KG	KHFZAN 11(8),132,77
IVN-MUS LD50:10 GM/KG	KHFZAN 11(8),132,77
IVN-CAT LD50:10 GM/KG	RPTOAN 47,205,84
UNR-MAM LD50:>10 GM/KG	RPTOAN 44,22,81

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.

MAY CAUSE IRRITATION.

EXPOSURE CAN CAUSE:

CNS STIMULATION

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,

CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

SOLID

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,

AND NITROGEN OXIDES.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.
CAUTION:
AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

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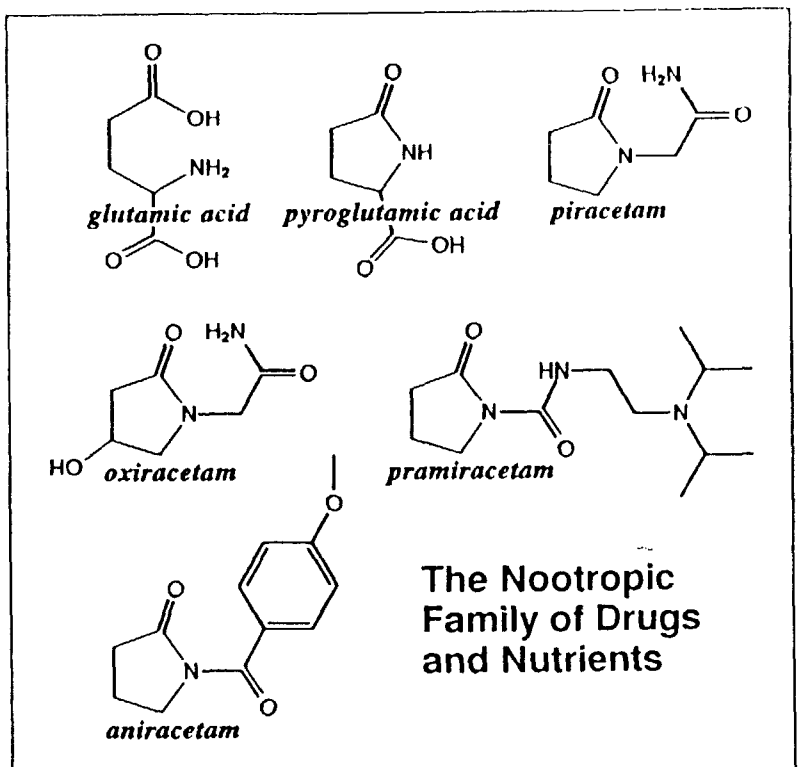
Piracetam Update

This unique substance is probably the most popular smart drug for normal, healthy people. We've received many positive comments about piracetam in the smart-drug fan mail. Some of the most interesting of these piracetam stories (and a couple of mild caveats) are included in the Smart Drug Users chapter of this book.

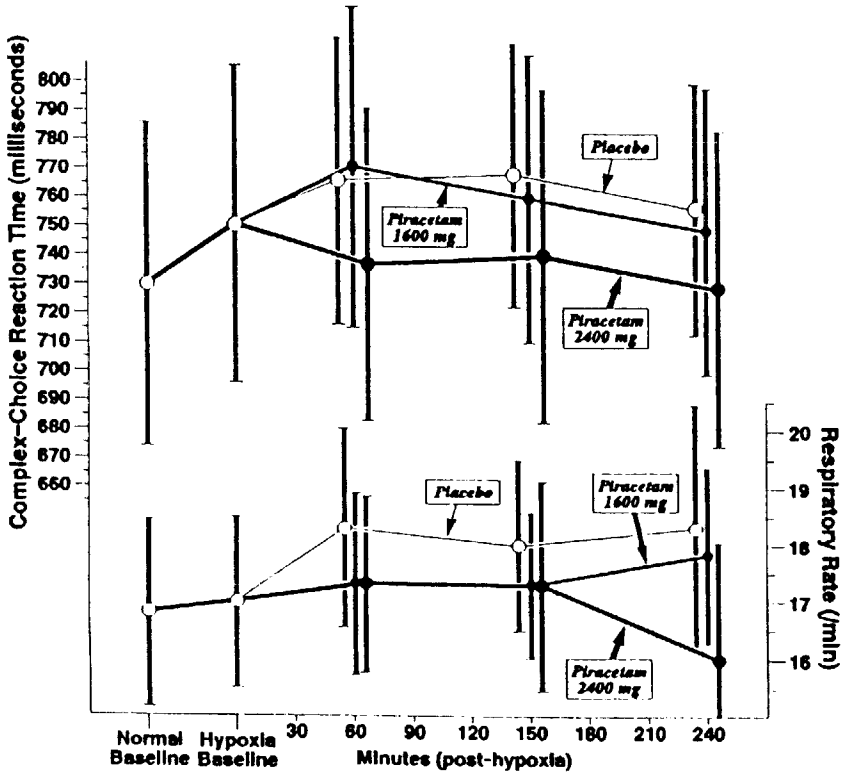
In the three years since *Smart Drugs & Nutrients* was researched and published, over 150 papers have appeared in the world's scientific literature which describe human studies of piracetam. Piracetam is, in fact, a broadly effective enhancer of many



aspects of human performance. The studies presented in this chapter clearly indicate the breadth of piracetam's clinical application. These studies amply illustrate piracetam's benefits for normal, healthy adults, normally aging elderly adults, and people suffering from overt cognitive disorders like senility and Alzheimer's disease.

Piracetam and Weekend Athletes

The ability of piracetam to reduce metabolic stress under low-oxygen conditions was investigated by Schaffler and Klausnitzer in 1988. The researchers induced hypoxia (low oxygen levels) in healthy young men (early 20s to early 30s) by reducing the oxygen content of the laboratory air that they breathed by about half (10.5% instead of 20% oxygen). This resembled "the



oxygen supply at an altitude of about 5300 meters" (17,400 feet). The degree of cognitive impairment due to the low oxygen levels was investigated, and the ability of piracetam (in single doses of 1600 mg or 2400 mg) to prevent this impairment was measured (see opposite figure). Half of the group was given a placebo.

Various tests of reaction time were performed, and in all cases, the piracetam-treated group performed better. Best results were obtained at the higher dose (see opposite figure, upper data points). The increased breathing rate that is usually seen under low oxygen conditions was significantly reduced by a single dose of piracetam (lower data points).

The significance of these results is that normal, healthy people who travel from lower altitudes to higher altitudes for physical activities that require stamina, coordination, concentration, and muscular output are likely to greatly benefit from piracetam. Skiers, take note! Smart-drugged skiers on vacation are probably less likely to injure themselves or someone else, and may be more likely to enjoy their vacation. Piracetam will probably not only make high-altitude sports safer, but is likely to improve performance as well.

Other high-altitude activities likely to be safer with piracetam include mountain bicycling, backpacking, rock climbing, hang gliding, and bungee jumping. And piracetam is likely to improve performance of the sport.

All of these activities involve some risk. Statistically speaking, compared to taking piracetam these sports are absolutely throw-caution-to-the-wind dare-devilish. Recently a bungee jumping trainer forgot to attach his own bungee to the mooring and jumped to his death. Would he have forgotten if he had taken piracetam? The research points to a decrease in the odds of making just this kind of error.

Piracetam for Cigarette Smokers

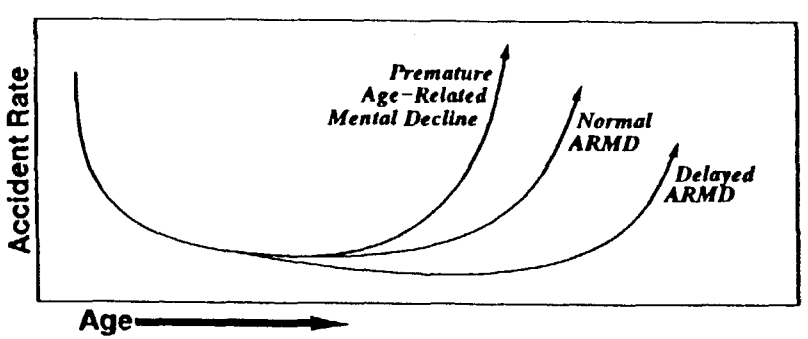
Of even more potential significance is the possibility that other disease conditions resulting from low oxygen levels in the blood

may also be alleviated by piracetam. For example, a two-pack-per-day cigarette smoker at sea level has the oxygen levels of a person at 10,000 feet. Also, many clinical conditions like atherosclerosis (occluded arteries) and many pulmonary diseases (especially emphysema) cause reduced blood and brain oxygenation. Piracetam may greatly relieve the adverse effects of oxygen shortage in these conditions.

Driving Skills in Elderly Motorists

Statistically, middle-aged drivers have the lowest accident rates. The rate of age-related accidents can be represented by a graph with a U-shaped curve (see illustration below) with the highest values in the late teens (learning to drive) and early twenties (learning traffic judgment), the lowest values in middle age (maximum skill, experience and judgment), and higher levels again at advanced ages (impaired vision, hearing, reaction time and/or judgment).

One study of elderly drivers (average age 62.7 years) showed slightly diminished performance in "driving tasks" as compared to middle-aged drivers (average age 40.6 years). This decrement was characterized by significantly diminished performance in sign observance, lane discipline, hesitant driving, technical handling, and "junction alertness" (leading to "twice as many risk situations which required driving-instructor intervention"). No differences in speed or safe-distance behavior were noted between the groups.



Could piracetam alter the shape of the accident curve and alleviate these decrements in older drivers by delaying the onset and slowing the progression of age-related changes?

A recent study conducted at the University of Cologne in Germany was performed to answer this question [Schmidt, 1991]. The researchers examined the driving skills of 101 elderly drivers with "reduced reaction capacity." In a randomized, double-blind, placebo-controlled study, in real-traffic conditions, those patients treated with piracetam exhibited significantly improved performance. Over the six-week test period, piracetam-treated drivers' "sign-observance" scores improved from 77.08% pre-treatment to 84.16% post-treatment.

This study indicates clearly that some of the age-related reductions in driving performance can be improved by piracetam. In only six weeks, the piracetam-treated drivers improved 7.08% on the sign-observance test. Of particular interest is the authors' note that "*all* of the drivers who scored less than 80% improved when treated with piracetam." This indicates that piracetam is most helpful in those people with the greatest driving impairment.

The number and percentage of elderly drivers in developed countries is increasing, as birth rates drop and life-expectancy increases. The extent to which widespread piracetam use by elderly drivers might diminish the rising costs of accidents caused by elderly drivers is not yet known, but it is certainly worth investigating.

Changes in Attitudes

Only three years ago, smart-drug critics were focusing on the lack of human testing in normal, healthy individuals. They said, "just because piracetam corrects cognitive deficits caused by disease doesn't mean it will correct cognitive deficits caused by aging, or that it will enhance cognitive abilities in healthy

people." However, increasing data now confirm that piracetam does, in fact, improve cognitive performance in normal people.

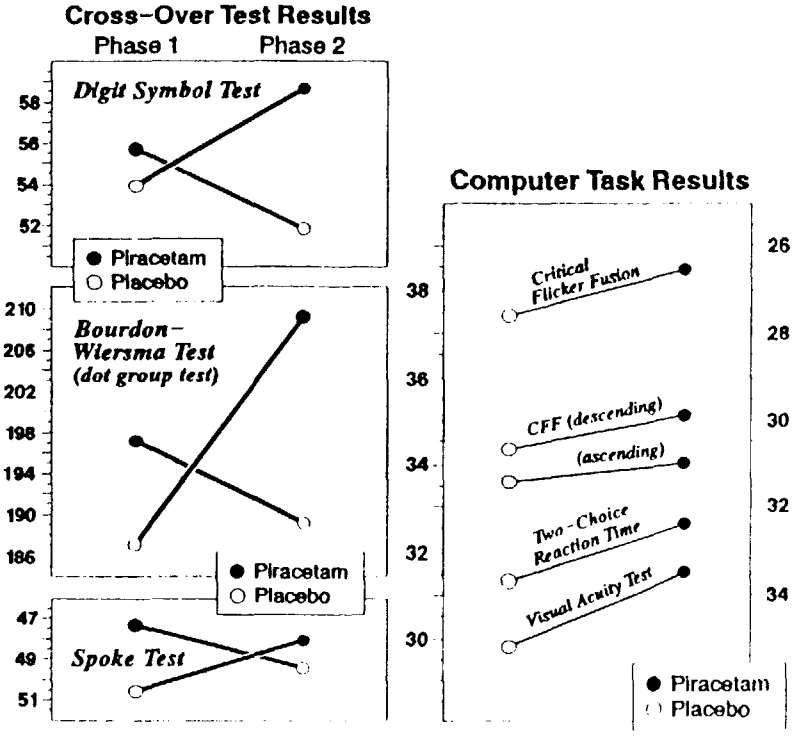
One of the first pioneering studies to investigate this possibility was conducted 17 years ago in Sweden long before the complaints of smart-drug critics [Mindus, 1976]. These researchers selected late-middle-aged test subjects (50 years and older) of above average intelligence (their IQs averaged above 120) and who were otherwise healthy (none had any clinical signs of rapidly deteriorating mental abilities).

All 18 test subjects reported "slight but seemingly permanent reduction for some years in their capacity to retain or recall information" (AAMI). They all had developed compensatory strategies and behaviors to continue in their highly demanding jobs, such as "taking notes" and "working slower." All in all, these subjects were a good cross-section of the more productive and accomplished senior members of the work force.

The researchers employed a double-blind, cross-over study. Half of the test subjects were given placebo for the first four weeks (phase 1), and piracetam (4.8 grams daily) for the second four weeks (phase 2). The other half were given piracetam first, and placebo second.

The subjects then took a number of performance tests, including computer-based tests. In all phases of testing, piracetam scores were higher. In the cross-over phase, all subjects who switched from placebo to piracetam improved in score, and all subjects who switched from piracetam to placebo lowered in score (see the graphs below).

The computer-test results were converted into like-magnitude units to illustrate the similarity of the performance increases from piracetam. It can be seen that all five computerized tests showed identical magnitude gains. This is certainly a striking observation, given the selective effects of some other smart drugs. Piracetam and other nootropic drugs seem to produce positive effects in many aspects of mental function.



Claims that smart drugs have not proven effective on normal, healthy people are clearly wrong. Such allegations are not based on science, but rather on the personal prejudices of the accusers and their unfamiliarity with the scientific literature.

Cognitive Enhancement in Senility

Although some critics may criticize the use of smart drugs to treat AAMI, many acknowledge that smart drugs *are* effective in the treatment of overt senile cognitive impairment. In a recent study of 84 geriatric patients with non-vascular senile cognitive deterioration, piracetam was found to be better than a placebo at enhancing several cognitive abilities, including attention, memory, and behavior [Fioravanti, 1991]. Dosages of 6 grams per day appeared to be more effective than 3 grams

per day. However, once optimum benefits had been obtained on the 6-gram-per-day dose, the 3-gram-per-day dose was adequate to maintain the cognitive gains induced by the higher dose.

Cognitive Performance in Epileptics

Anti-epileptic medicines often exhibit cognitive side effects in the inverted-U dose-response manner. For example, at low doses, many anti-epileptic drugs improve cognition scores. However, at the high doses often necessary to control epileptic seizures, anti-epileptic drugs can cause profound cognitive impairment.

In a new study of the cognitive properties of piracetam in epileptic patients, piracetam was found to significantly improve cognitive test results without interfering with the efficacy of anti-epileptic medications. Patients taking one anti-seizure drug (carbamazepine) appeared to have even greater seizure protection when the carbamazepine was combined with piracetam [Chaudhry, 1992].

New Research Trends

Recent research into the mechanisms of nootropic drugs (drugs in the same class as piracetam) is shedding light on the crucial question, "How does piracetam work?" New findings point to a number of modes of action, including 1) stimulation of glucose metabolism, 2) increased ATP turnover, 3) increased 'internal messenger' (cyclic AMP, or cAMP) levels, 4) enhanced phospholipid levels, 5) increased protein biosynthesis, and 6) increased cholinergic and dopaminergic stimulation. Nootropics also seem to produce resistance to several neurotoxic substances, and stimulate learning through influences on the hippocampus and cortex. Oxygen utilization by the brain appears to be significantly enhanced. [Schaffler, *et al.*, 1988].

The Recognition Piracetam Deserves

It is long past time to recognize and acknowledge that piracetam does indeed enhance cognition in both normal healthy people *and* the cognitively impaired. In 1990, piracetam sales from one brand alone (Nootropil, UCB) topped *one billion dollars* worldwide. According to UCB's annual report, Nootropil sales are still increasing, years after their patent on piracetam has expired, and numerous competitive generic piracetam products have entered the market. After decades of completely safe use, and millions of prescription and over-the-counter sales in many countries, we believe that it's time for the United States to join the rest of the world in approving piracetam for its citizens. Piracetam's absence of any known toxicity makes it an ideal candidate for over-the-counter status.

Precautions

Piracetam may increase the effects of certain drugs, such as amphetamines, psychotropics, and Hydergine, as previously stated. Adverse effects are extremely rare, but include insomnia, psychomotor agitation, nausea, gastrointestinal distress, and headaches. Piracetam has no known toxicity or contraindications.

Dosage

Piracetam is supplied in 400 mg or 800 mg capsules or tablets. The usual dose is 2400 to 4800 mg per day in three divided doses. Some literature recommends a high "attack" dose be taken for the first two days. We have noticed that often when people first take piracetam they do not notice any effect at all until they take a high dose (approximately 4000 to 8000 mg). Thereafter, they may notice that a lower dosage is sufficient. Piracetam takes effect within 30 to 60 minutes.

Note that piracetam seems to synergize with other smart drugs. If piracetam is combined with other smart drugs, the dosage of one or more drugs/nutrients may need to be reduced.

Sources

Piracetam is not available in the U.S. but can be easily ordered from most overseas mail-order pharmacies. An up-to-date listing of such overseas sources is maintained by CERI (see the tearout card at the front of this book).

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Vitamin Update

When *Smart Drugs & Nutrients* was written in 1990, vitamins were still considered "fringe science" by many in the medical profession. Nevertheless, we reviewed in that book some of the scientific evidence on the cognitive-performance-enhancing benefits of vitamins.

Since the publication of *Smart Drugs & Nutrients*, there seems to have been a paradigm shift away from the bad old days of physicians warning against vitamins, to a new consensus in the scientific and medical community that vitamins are potent disease fighters and potential aging-retardants.

On April 6, 1992, *Time* magazine published a cover story on vitamins, proclaiming that, "New evidence shows they may help fight cancer, heart disease, and the ravages of aging." A mere ten years ago, such a story would have generated a storm of protest from medical authorities. Today, the ever-mounting evidence for the abilities of nutrients to prevent and treat disease is so overwhelming that only a few die-hard anti-vitamin medical "authorities" remain vocal critics. Vitamins are now mainstream.

As Barbara Walters commented on ABC's *Nightline*, "There was a time when doctors said, 'Eat a balanced diet and you don't have to take vitamins.' Now we are learning that this vitamin or that vitamin might help prevent cancer." At the 1992 *American Aging Association* Conference in San Francisco, one researcher volunteered that nearly everyone in the field of gerontology (the study of aging) is now taking megadoses of vitamins. Ten years ago, only a few were.

Approximately half of all Americans take vitamin supplements and about half of those take daily supplements. Americans spend $3.3 billion on vitamins and nutrients every year — and that figure is growing.

Critical Reviews™ in Neurobiology, 10(3&4):357–370 (1996)

Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine

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ABSTRACT: This review is meant to serve several purposes. First, it surveys the preclinical and clinical profiles of piracetam-like nootropics. Second, the conditions under which the nootropics are active in preclinical studies are identified and analyzed with a view to finding a common denominator that could explain the observed effects. Third, the clinical profile is examined, on the one hand to assess whether these drugs are in fact active in humans, and on the other to determine how the clinical effects of the nootropics compare with those of tacrine. Lastly, the clinical data are then further scrutinized to assess whether they fulfill the expectations based on the preclinical findings.

KEY WORDS: Nootropics, piracetam, oxiracetam, pramiracetam, aniracetam, tacrine, preclinical, clinical, responders, nonresponders.

INTRODUCTION

The discovery of piracetam[1] shook faith in Paracelsus' famous axiom, "dosis facit venenum." This memory improving substance not only was devoid of other biological activity but also had no toxic effects whatever at doses up to grams per kilogram of body weight. Even today, nearly 30 years after the discovery, the "nootropic" class of substances[2] newly created to accommodate piracetam still splits pharmacologists into two camps. For some, the absence of toxicity indicates a lack of any pharmacological action, while others see it as pointing to a new therapeutic approach. Depending on the observer's standpoint, either the nonresponders in clinical trials testify to the inefficacy of these agents, or the responders bear out their activity. This controversy has severely hindered genuine scientific progress and has prevented full advantage from being taken of the therapeutic potential of the nootropics.

Piracetam is long since not the sole representative of this class. In the meantime a great many structurally related active compounds have been synthesized, confirming the need to assign the nootropics to a category of their own. The term *nootropic* derives from the Greek words *noos*, mind, and *tropos*, toward, and thus reflects not a class of chemical structures, but the supposed effect of these compounds on cognitive processes. It is consequently inevitable that a certain tendency exists to attach this label to all memory-enhancing substances (for a comprehensive review, see references 3,4).

The present review is devoted entirely to the piracetam-like preparations and focused on their direct nootropic effects, i.e., the spectrum of effects on the memory of intact animals, rather than on their mechanism of action. The latter aspect was the subject of recent reviews.[4,5] Since it is impossible to assess the activity of a substance without recourse to reference compounds, both the preclinical and the clinical results are discussed on that basis. Tacrine, the only compound registered for the treatment of Alzheimer's disease, is taken as the sole reference drug for comparisons of the clinical results.

II. PRECLINICAL EFFECTS OF THE NOOTROPICS

Although the first observed effect of piracetam on the central nervous system (CNS) was inhibi-

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tion of central nystagmus in the rabbit.[1] further findings made during the past 25 years showed that its main action consists in the improvement of cognitive functions. The earliest studies were concerned with pharmacological modulation of the amnesiogenic effects of a cerebral electroshock. When Giurgea and Mouravieff Lesuisse[6] demonstrated that piracetam reduced the disrupting influence of an electroshock on the orientation of rats in a water maze, this effect was taken as an indication that piracetam improved memory consolidation. Over the years, this antiamnestic action of the piracetam-like preparations has often been confirmed. Studies with aniracetam,[7] oxiracetam,[8] pramiracetam, and a series of analogues[9] all showed a distinct protective action against the effect of electroshock on memory.

This rather indirect indication of a nootropic action was supplemented and reinforced by findings showing a direct memory-enhancing effect. A great many results emerged from experiments in avoidance learning. For example, aniracetam and piracetam[10,11] and oxiracetam[12] were found to exert direct effects on the acquisition and retention performance of rats and mice in both passive- and active-avoidance paradigms. Of particular value were the results of investigations in which the preparations were administered immediately after the learning trial ('post-trial'). In such conditions, the animal experiences the learning situation without being under the influence of the drug and is likewise uninfluenced during the retention test. Any demonstrable effect can then be ascribed to a direct action of the substance on memory processes that outlast the learning situation for some time. Several experiments showed that nootropics can improve the memory under such conditions.[13,14]

The learning situations in which piracetam-like nootropics were active were not limited to experiments involving avoidance behavior. Pramiracetam had positive effects in a place navigation task[15] and was also found to improve the acquisition rate in a 16-arm radial maze,[16] whereby the effect related exclusively to reference memory, not working memory. A slight, but significant, effect of pramiracetam was also demonstrable in a delayed alternation trial.[17] Aniracetam likewise displayed positive effects in a radial maze[18] and a matching-to-sample test.[19] Moreover, it was found that piracetam and pramiracetam improved performance in an object recognition test.[20] Aniracetam[21] and oxiracetam[22] were observed to have positive effects in a social-recognition test in rats.

In sum, from the data so far available it can be concluded that the nootropics exert a distinct memory-enhancing effect in various learning situations and in different animal species. In most experiments the acquisition or storage of the information occurred under the influence of the drug and retention was assessed after an interval of at least one day. Effects on short-term retention have been described (e.g., in a delayed-alternation or delayed matching-to-sample task, and social recognition after short intervals), but these observations have not yet been confirmed.

A. Which Memory Processes Are Facilitated by Nootropics?

The many experimental situations in which nootropics have been asserted to exert a memory-enhancing action raise the question whether there is a common denominator underlying all these effects: such as a similar target process, or whether even the whole spectrum of activity of the nootropics is the same. The available evidence would suggest that their activity spectra are not identical, but at least very similar, inasmuch as all these preparations improve passive avoidance[23,24] and active avoidance,[12,25] and all of them improve retention performance, even if administered post-trial.[13] The results of studies with post-trial administration reveal a high degree of concordance: it has been demonstrated that all four prototype nootropics—oxiracetam, piracetam, pramiracetam, and aniracetam—can enhance memory even if administered up to eight hours after the learning trial. After an interval of 16 hours, an effect was no longer evident.[13,14] It can be inferred that under these conditions all these drugs affect a process that outlasts the learning situation by more than 8, but less than 16, hours (a hypothesis relative to the process affected is advanced in reference 14). The improvement in retention performance in all these experiments was assessed after 24 or 72 hours, i.e., at a time when the memory content is generally supposed to be

sent in a long-term form. It was further shown that the retention performance of mice exposed to a learning situation after receiving a single dose of oxiracetam was distinctly better than that of controls even after one, two, or four months.[26] This finding lent additional support not only to the assumption that the substances ultimately improve long-term memory (LTM) storage, but also to the supposition that after intervals of 1 to 120 days memory is based on the same substrate.

Also in accord with the hypothesis that the nootropics improve LTM storage are the responses evoked by pramiracetam[16] and aniracetam[18] in the radial maze, in which solely effects on reference memory were observed. Thus, the only effects remaining to be explained are those noted in the delayed matching-to-sample test[6] and the improvements seen in the social-recognition test after a two-hour interval.[7] If these effects hold good for all nootropics, they can be taken as an indication that the facilitation of LTM is just one aspect of a whole range of activity; if not, they could indicate differences in the activity spectra of the various nootropics. Many indications of differences have been observed. Comparative studies of pramiracetam and etiracetam, for example, showed that only etiracetam had effects on memory retrieval.[27] Moreover, a long list of experiments indicate quantitative and qualitative differences in the biochemical activity spectrum of piracetam-like nootropics[4,28–30] so that there is hardly cause to expect such drugs to display an identical spectrum of activity.

Thus, the most obvious common feature of the nootropics is their capacity to facilitate LTM storage. This conclusion is consistent with the majority of the available preclinical results. Despite the high degree of similarity in the observed effects, some experimental findings do appear to indicate differences in the activity spectra.

B. Effects of Nootropics Compared with Those of Other Memory Enhancers

Comparative studies have revealed that there are no differences among the LTM effects of the four prototype nootropics—oxiracetam, piracetam, aniracetam, and pramiracetam—the cholinomimetics—tacrine, physostigmine, and arecoline—the ACE inhibitor captopril, the calcium antagonist nimodipine, and the gamma-aminobutyric acid B (GABAB)-receptor antagonist CGP 36742 in a passive-avoidance paradigm (Figure 1). It was subsequently observed that all these LTM effects were equally steroid sensitive; i.e., experimentally elevated aldosterone or corticosterone levels suppressed the effects of all these memory enhancers to the same extent.[23,31] The pharmacodynamics of oxiracetam, arecoline, CGP 36742, and captopril were similar: there was an 8-hour drug-sensitive window after the learning trial (Figure 2). Note that the memory-enhancing effects induced by captopril, CGP 36742, and the muscarinic cholinergic agonist arecoline followed almost exactly the same pattern as that of oxiracetam, in that they were not immediately detectable, i.e., not in evidence as soon as the animals showed signs of retention. At least a further 16-20 hours elapsed before it emerged (Figure 3). This surprising concordance in the findings strongly suggests that all four of these drugs affect the same process.

By analogy with the results obtained with oxiracetam, it seems reasonable to assume that the process in question is LTM storage. This conclusion is proposed purely as a possible common denominator and must not be construed as an exhaustive description of the activity spectrum. The totality of the cholinergic effects induced by physostigmine activates the brain quite differently from blockade of the angiotensin-converting enzyme or the effects of piracetam. It is consequently logical that, despite the common effects, differences in the activity spectra are to be expected. Such differences have been observed in experimental studies: only captopril facilitated memory retrieval after a 2-month retention interval; piracetam did not.[32] Piracetam and pramiracetam improved performance in an object recognition test,[20] whereas physostigmine had no such effect.[33] In contrast to pramiracetam,[16] and aniracetam,[18] physostigmine had no memory-enhancing effect in radial-maze tests.[34] It must, however, be conceded that these results are not derived from comparative studies.

In summary, all memory-enhancing compounds display similarities in their activities and in the intensities and dynamics of their effects in LTM experiments. The effects are steroid sensitive and become detectable only after a lapse of

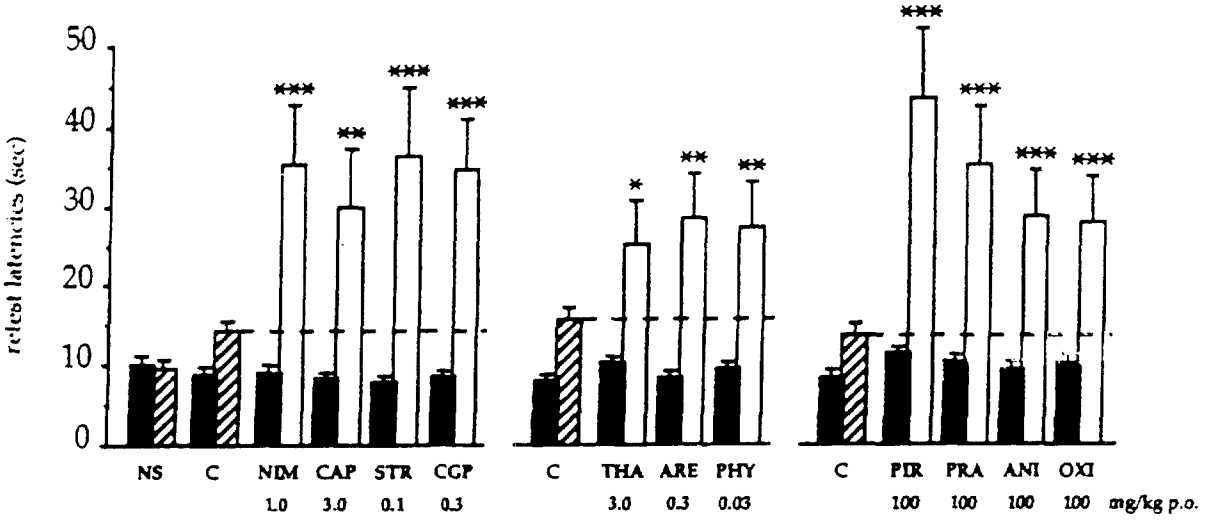

FIGURE 1. The effects of various memory-enhancing substances on the retention performance of mice in a passive-avoidance task. Mice were given footshock for leaving a "safe" small platform in the center of a grid floor. The spontaneous ("baseline") latencies to step onto the grid were measured. Retention (i.e., the retest latencies) was assessed 24 hours later. The histograms represent the step-down latencies in seconds. Solid columns: baseline latencies; blank columns: retest latencies of drug-treated animals; hatched columns: retest latencies of the vehicle-treated controls. NIM: nimodipine; CAP: captopril; STR: strychnine; CGP: CGP 36742 (GABAB antagonist); THA: tacrine; ARE: arecoline; PHY: physostigmine; PIR: piracetam; PRA: pramiracetam; ANI: aniracetam; OXI: oxiracetam. Physostigmine was given orally 30 minutes, all other substances, two hours, before the learning trial. Optimal doses for memory improvement were determined in independent pilot experiments. Prolongation of the retest latencies (in comparison with the no-shock controls [NS] and baseline latencies) indicates learning. Prolongation of the retest latencies in comparison with the retest latencies of the vehicle-treated controls indicates drug-induced memory improvement. N = 25 mice/group. $^{*}2p<0.05$, $^{**}2p<0.01$, $^{***}2p<0.001$ (Mann-Whitney U-test)

several hours. There are, nevertheless, experimental findings indicating differences in activity spectra, both within and between the various groups of memory enhancers, above all in tests not related to LTM.

III. THE CLINICAL EFFECTS OF THE NOOTROPICS

Any attempt to pinpoint common features in the available clinical data on these compounds quickly runs into certain problems. One major difficulty is due to the heterogeneity of the patient populations. Studies have been carried out in probable cases of Alzheimer's disease,[34–38] in a mixed population of Alzheimer and multiinfarct dementia patients, [ ] in multiinfarct patients,[43] in patients with psychoorganic syndrome,[44–48] in aged volunteers,[49] in students,[50] in epileptic patients,[51] in dyslexic schoolchildren,[52] in patients suffering from effects of exposure to organic solvents,[53,54] in victims of head trauma,[55,56] in patients with Korsakoff's syndrome,[57] and even in patients with artificial pacemakers.[58] The numbers of patients in each study ranged from 4[56] to 289.[41] Durations of treatment also varied greatly: for example, 9 days,[58] 4 weeks,[43,45] 3 months,[39–41,46,47,51] and up to 1 year.[34] The study design was variously open,[59,60] single-blind,[43,61] double-blind,[34,39,40] parallel with placebo controls[36,39,41,42] or active controls,[62,63] crossover,[37,54] or enriched:[35] even comparisons with historical controls were used.[64]

No less heterogeneous was the clinical and psychometric instrumentarium employed to assess the effects. Besides neuropsychological tests and scales, psychophysiological tests were also used. The quality of reporting differed greatly. In some studies, the test used is not simply mentioned but described exactly (e.g., reference 40), whereas in others the sole indication of the nature of the effect observed and the methodology applied was the single word *memory*.[53] In evaluating the effects, the psychometric tests were some-

times supplemented by staff-rated scales[47]; sometimes only staff-rated scales were used,[65] or even just the clinician's global impression was given.[66] The study design was entirely adapted to demonstrating the existence of an effect of the preparation in patients.

Surprisingly, at first glance, scrutiny of the results of the published clinical studies reveals that the majority (more than 60%) of the reports are positive; i.e., the authors conclude from their findings that the treatment was effective. Villardita et al.,[39] for instance, showed that after three months the 30 patients treated with oxiracetam in a double-blind, parallel-design study displayed significant improvements in 9 of the 18 tests used compared with their baseline performance before the beginning of treatment. The 30 placebo-treated patients, on the other hand, showed no improvements, and even performed significantly worse in two of the tests. The positive effects were particularly clear-cut in the Mini Mental State Examination (MMSE), the Auditory Continuous Performance Test (ACPT), Rey's 15 Words Test, the Block Tapping Test (BTT), the Mattis Word Fluency Test, Luria's Alternating Series, and the Instrumental Activities of Daily Living Test (IADL-E).

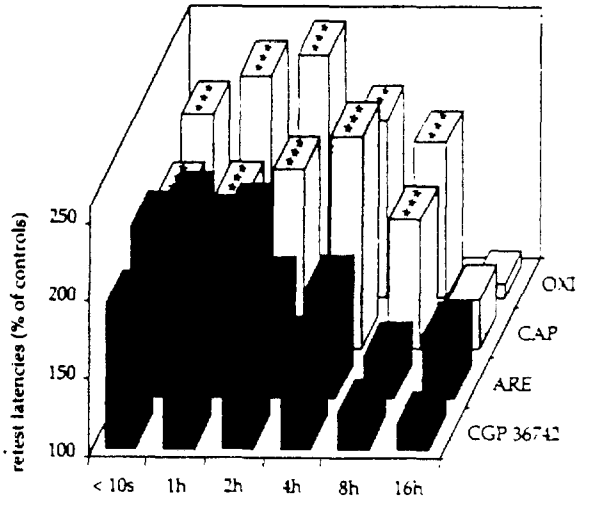

FIGURE 2. The effects of various compounds on memory if administered at various intervals after the learning experience. The animals were exposed to the passive-avoidance situation, and after the indicated intervals (<10 seconds, 1, 2, 4, 8, 16 hours) treated with optimal doses of the memory enhancers. Retest was performed after 72 hours. The columns indicate the prolongation of the retest latencies (in percent of the vehicle-treated matched controls). Prolonged latencies indicate better memory. ARE: arecoline; CAP: captopril; OXI: oxiracetam. *2p<0.05, **2p<0.01, ***2p<0.001.

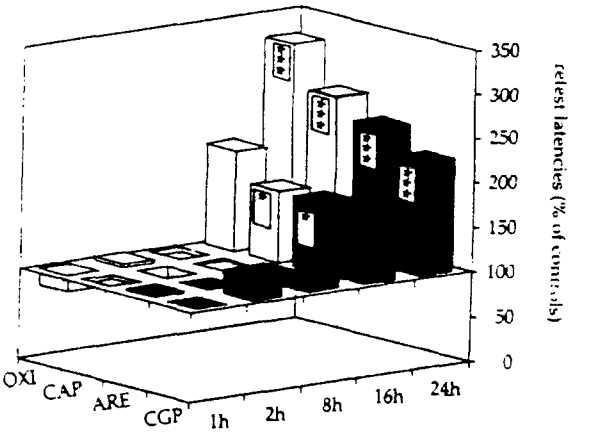

FIGURE 3. The emergence of the memory facilitation effect induced by the nootropic oxiracetam (100 mg/kg), the ACE-inhibitor captopril (3 mg/kg), the muscarinic agonist arecoline (0.3 mg/kg), and the GABAB-receptor blocker CGP 36742 (10 mg/kg). The animals were trained in a passive-avoidance situation and treated immediately thereafter. Retention performance was measured at various intervals (1, 2, 8, 16, or 24 hours) after training and treatment. The columns indicate the drug-induced prolongation of the retest latencies (in percent of the vehicle-treated controls). *2p<0.05, **2p<0.01, ***2p<0.001. Prolonged latencies indicate better memory. All treatments were given intraperitoneally immediately after the learning trial (from Mondadori et al., *Proc. Natl. Acad. Sci.*, 91, 2041, 1994).

Senin et al.[38] performed a study with aniracetam, using a test battery different from that applied by Villardita. At the end of the 6-month treatment period the authors found significant improvements of performance in all 18 parameters assessed. As in Villardita's study, positive effects were recorded in Rey's 15 Word Test. Note that besides effects on cognitive parameters, these authors also observed distinct effects on behavioral parameters. The 6-month study with aniracetam performed by Parnetti et al.[67] according to a similar design yielded practically identical results: in 17 of 18 tests, aniracetam improved the patients' performance. In this comparative study the activity spectrum of aniracetam in some tests was distinctly different from that of piracetam. Unlike aniracetam, for instance, piracetam displayed no effects in Rey's 15 Words Test, in the Toulouse Pieron Test, and in the

Raven Test. According to the Sandoz Clinical Assessment Geriatric (SCAG) Scale, however, the effects were nearly identical. Bottini et al.[40] observed distinct effects of oxiracetam in five of eight cognitive tests. In particular, there were significant positive effects on verbal fluency, similar to those described by Villardita et al., and the retention of a short story (after a delay of 10 minutes) was also improved. In the 12-month study with piracetam conducted by Croisile et al.,[34] indications of a retardant effect of the drug on the progress of mental decline were noted: in the placebo group a significant deterioration was evident at the end of the year in 8 of 14 tests, whereas in the piracetam group negative results were recorded in only one test. In contrast to the findings of Senin et al. and Parnetti et al., direct comparisons of the performance of placebo-treated and piracetam-treated patients yielded scarcely any statistically significant results. The study carried out by Maina et al.[41] in the largest population samples of all (N = 144 + 145), positive (good to very good) effects of oxiracetam were recorded in 90 of 145 patients (global evaluation), whereas, according to the same criteria, only 27 of 144 placebo-treated patients were rated as showing good or very good responses. Only 51 of 144 patients taking oxiracetam as against 107 of 144 receiving placebo were rated as showing no effect or a poor effect. Note that the patients in this study, in contrast to those in the study by Villardita et al., showed positive effects in the IPSC-E (Inventory of Psychic and Somatic Complaints, Elderly). Statistically significant increases in the IPSC-E scores were also recorded in the 6-month study performed by Mangoni et al.,[36] while no changes were seen in the placebo-treated controls.

Itil et al.[46] also reported significant effects of oxiracetam in the IPSC-E, not in Alzheimer patients, but in diagnostically less precisely defined cases of organic brain syndrome (OBS). These effects were more pronounced than the corresponding effects of piracetam. Such changes in the IPSC-E suggest that oxiracetam exerts effects that can be manifest as an improvement in the quality of life of the patients. The results obtained by Saletu et al.[45] in their study of a similar patient population were far less distinct: apart from an improvement in verbal memory, only the overall score in the SCAG was significantly better (the IPSC-E was not used). The duration of treatment in this study was only four weeks. More modest still were the clinical effects noted in the study of piracetam performed by Abbuzahab et al.[48] in OBS patients (geriatric memory): apart from a slight overall improvement, no relevant effects were observed. Much more pronounced positive effects emerged from the investigation by Moglia et al.[42] In this parallel-design study in 21 + 22 OBS patients, these authors showed that oxiracetam induced an overall improvement in cognitive and behavioral parameters. Particularly notable were the significant improvements seen in the Benton Visual Motor Retention test (as also used by Itil et al.) and in the arithmetical part of the Wechsler Adult Intelligence Scale (WAIS). The conclusion that the general well-being of the patients treated with oxiracetam had improved is consistent with the many global clinical assessments, as exemplified by a 3-month placebo-controlled study in 60 patients with two doses of piracetam carried out by Chouinard et al.[47] In this study, the results of the monthly evaluations by the nursing staff (Nurses Global Improvement Rating Scale) clearly indicated an improvement in the patients' sense of well-being, whereby particular emphasis was placed on alertness, socialization, and orientation. Another study by Foltyn et al.,[65] showing aniracetam to have been effective over a duration of four weeks in N = 30 +30 patients, was based exclusively on staff ratings.

Nootropics were also tested for efficacy in completely different clinical indications. McLean et al.,[56] for example, examined pramiracetam in four patients with head injuries or anoxia and showed that the drug exerted clear-cut effects on immediate and delayed recall. In patients with pacemakers, in whom the fixed heart rate often leads to diminished cerebral circulation and consequent disturbances of performance during exertion, piracetam was found to induce a slight improvement in psychomotor tests[58]; no cognitive tests were performed, however. In a study in epileptic patients with memory disorders, Aldenkamp et al.[51] observed no effects after 12 weeks, but all parameters measured revealed a trend favoring oxiracetam.

In some investigations, comparative evaluations were made of the effects of nootropics. In

the above-mentioned study by Itil et al.,[46] oxiracetam was found to have a slightly better effect on cognitive parameters than piracetam, whereas piracetam displayed a slightly better antipsychotic effect than oxiracetam. Although the greater efficacy of oxiracetam in regard to cognitive aspects was confirmed in the studies by Gallai et al.[61] and Ferrero,[63] these studies were not carried out under double-blind conditions and are consequently not admissible as valid scientific evidence. The same applies to the study conducted by Falsaperla,[62] in which the effects of oxiracetam were compared with those of deprenyl in Alzheimer patients. Here, both drugs improved the patients' performance above baseline levels in a whole series of tests, deprenyl emerging as the more effective treatment. Aniracetam was also shown to be slightly more active than piracetam in the study by Parnetti et al.[60]

In contrast to the many positive results reported, a 3-month study in Alzheimer patients performed by Green et al.[68] and using a broad battery of neuropsychological tests revealed no signs of efficacy of oxiracetam, either on the basis of group analyses or in individual patients. Similarly, a 3-month trial by Hjorther et al.[53] with a very extensive test battery gave no indication of any effects of oxiracetam: neither behavioral nor memory parameters showed any signs of improvement. Note that this trial was done in a special group of OBS patients, suffering from toxic encephalopathy following exposure to organic solvents. In full concordance with these results, Somnier et al.[54] detected no signs of efficacy of aniracetam in such patients. A notable feature of this study was that Somnier employed a crossover design. Other crossover trials have also revealed no positive effects. Lloyd-Evans et al.[44] were unable to detect any effects of piracetam in a 6-month double-blind trial in OBS patients. The 2 × 4-week crossover study with oxiracetam performed by Molloy et al.[37] in Alzheimer patients likewise showed no effects. In none of these crossover trials was the first drug/placebo phase evaluated separately as a parallel study. Negative results further emerged from an enriched-design study by Claus et al.,[35] who concluded from their results that pramiracetam is ineffective as a symptomatic treatment for Alzheimer patients. This rating was based on the scores achieved by 10 patients in the Alzheimer's Disease Assessment Scale (ADAS). In patients with alcoholic organic mental disorders also, a study conducted by Fleischhacker et al.[57] demonstrated no relevant improvement after treatment with piracetam.

Given the existence of studies with positive and others with negative results or overall ratings, one question that arises is what 'positive' or 'negative' means to the individual patients. As regards the positive studies, that question has already been answered, insofar as it was often mentioned that only a limited number of patients responded to the treatment (e.g., reference 41). Unfortunately, in the clinical studies with nootropics, only scant information is given about the frequency of significant therapeutic effects and the quality of such effects in individual patients. The fact that, despite many nonresponders, positive overall ratings were still reported would at least seem to justify the reverse question of how often individual responders were present even in the negative studies. For want of adequate information on responders and nonre-sponders in most double-blind studies, illustrative data must also be drawn from the results of open trials. In the study performed by Claus et al.,[35] the conclusion that piracetam was ineffective was based on the lack of significant effects in the ADAS in 10 patients. In fact, however, there was at least one responder with a reduction of more than four points in the ADAS and significant, drug-related improvements in both the Visual Selective Reminding Task (total and delay) and Logical Memory Immediate Recall. These effects were inevitably submerged in the calculations of the means values and statistical analysis. In the study by Baumel et al.[43] also, where the drug effects were rated as very modest, 4 of the 12 patients showed responses. In that the case reports were described as typical, this was a substantial effect from the viewpoint of the quality of life. This outcome is closely similar to the results of the open study in six patients by Dager et al.,[59] in which there was one definite responder. Irrespective of the extent to which the cited data were attributable to drug effects, they demonstrate the need for analyses of this nature.

It can be concluded that the piracetam-like nootropics can evoke significant effects in Alzheimer patients, becoming manifest on the

one hand in cognitive improvements and on the other in behavioral aspects. The effect appears to become more marked during prolonged treatment. The various nootropics differ in their activity spectra. In general, however, there were only a limited number of responders. The few efforts made to characterize this group of patients (e.g., reference 59) were unsuccessful.

IV. COMPARISON WITH THE CLINICAL EFFECTS OF TACRINE

Any attempt to characterize the clinical effects of the nootropics almost automatically necessitates a comparison with cholinomimetics. In contradistinction to the nootropics, cholinergic substances are used in Alzheimer patients, not because of their memory-enhancing effects in animals, but because of the existence of a cholinergic deficit in these patients.[69] In this respect, the patient population studied is homogeneous and, unlike the very mixed populations treated with nootropics, includes only (probable) Alzheimer patients. The group sizes are similar to those in the nootropic studies. The methodology used is more nearly uniform but different from that adopted for nootropics. The following section is confined to tetrahydroaminoacridine (THA, tacrine, Cognex®), a cholinesterase inhibitor and the only substance so far registered for the treatment of Alzheimer's disease.

The first study by Summers et al.[70] was conducted in three phases. In the first phase, the tolerability and efficacy of incremental doses of THA were assessed in 23 patients. THA was always administered in combination with lecithin. In a second double-blind, crossover phase, 15 of these patients were treated with the best or highest dose of THA, or with placebo, for three weeks, after which the treatments were switched. Only the 12 patients showing a clear-cut response to THA in the second phase went on to receive long-term treatment over periods ranging from 3 to 26 months (enriched design). The final assessment revealed distinct positive results (global assessment, orientation, Alzheimer deficit scale, names learning test), whereby only patients classed as Stages 3-4, but not Stages 5-6, on the Reisberg scale responded.

Most of the subsequent studies initially failed to confirm Summers' results. A crossover study conducted by Davies et al.,[71] for example, in which 10 patients were treated for up to four months, showed hardly any notable effects of the combined treatment with THA and lecithin. Only in 1 of 10 tests were positive results recorded. The same results were obtained by Chatellier et al.[72] In this crossover study with 67 patients, tacrine (combined with lecithin) was administered orally for four weeks. Apart from a slight improvement in the Physician's Score, THA was ineffective. Neither in behavioral scales (Stockton) nor in cognitive scales (MMSE) were any effects demonstrable. Similarly, in a crossover trial done by Gauthier et al.[73] over two 8-week treatment periods, the response to THA was limited to an improvement in the MMSE. Despite this improvement, the authors rated the effect of THA as clinically irrelevant. No effect whatever was observed by Molloy et al.[74] in a multiple crossover study with treatment periods of three weeks. Neither the overall evaluation nor a detailed analysis of individual patients revealed any indications of effects.

Positive results, on the other hand, were obtained in the trial conducted by Davis et al.[75] The 215 patients who had responded to tacrine in a preliminary crossover phase were subsequently treated for six weeks in a parallel study. By comparison with the placebo controls, the tacrine group showed a slight, but significant, decrease in mental decline (ADAS cognitive subscale). Two of the three quality-of-life assessment scales used indicated changes in favor of tacrine: Progressive Deterioration Scale (PDS) and Activities of Daily Living (ADL). The changes in the MMSE were slight and statistically not significant, and the clinician's global assessment (CGIC) likewise failed to detect any effects. In a similar, but more prolonged (12-week) parallel study by Farlow et al.,[76] very much the same results were obtained: the ADAS cognitive subscale indicated some retardation of cognitive decline, but the MMSE showed no changes. In contrast to the study by Davis, however, the physicians' and caregivers' global ratings were significantly better. In a crossover study by Eagger et al.,[77] in which 468 patients were treated for considerably longer (13 weeks) than those in Molloy's study,[74] the MMSE

and the AMTS (Abbreviated Mental Test Score), but not the ADL, revealed an effect of tacrine. The effects in the MMSE were consistent with the findings of Gauthier et al.,[73] but not with those of Farlow et al.[76] and Davis et al.[75]; the absence of effects in the ADL were at variance with the results observed by Davis et al.[75]

Recent studies disclosed the entire range of possible effects. Distinctly positive effects emerged from a 30-week parallel study by Knapp et al.[78] In this study with an initial population of 663 patients, all three primary outcome measures (ADAS cognitive subscale, Clinicians' Interview-Based Impression, and Final Comprehensive Consensus Impression) showed significant effects of tacrine. In addition, positive effects, among others, were demonstrated by the Progressive Deterioration Scale and the MMSE, but not the ADL. The effects indicated by the MMSE were in agreement with those noted by Gauthier et al.,[73] Eagger et al.,[77] and Davis et al.,[75] but contrary to those seen by Farlow et al.[76] and Molloy et al.[74] Although consistent with the findings of Eagger et al.,[77] the absence of effects in the ADL conflicted with those of Davis et al.[75] Exactly the opposite, i.e., no indications of any effect whatever, emerged from the study by Maltby et al.[79] with an initial population of 57 patients and a 36-week duration of treatment. Neither the Caregivers' rating-based scales nor the cognitive scales showed signs of changes. Halfway between positive and negative results lie the findings reported by Wilcock et al.[80] In a 2 × 3-month crossover study in 41 patients these authors noted positive trends in favor of tacrine, but statistically the differences were scarcely significant. In a study with 154 patients, Wood et al.[81] likewise merely observed positive trends, but there was no significant effect of tacrine in the overall group analysis. The results nevertheless indicate that there were individual responders. The same applies to a 3 × 6-week crossover study of Alzheimer patients conducted by Gustafson[82] in which there was no detectable overall effect, but individual responders were noted. It is, above all, the enrichment studies that confirm the existence of a subset of responders, although even after the enrichment not all patients respond to the treatment. In the light of these findings and in view of the need to optimize therapy, it is surprising that scarcely any efforts have been made to establish a pharmacological, biochemical, and endocrinological profile that would serve to identify likely responders.

To sum up, although there are clear indications that cholinesterase inhibitors do exert clinical effects, it is equally clear that only a certain number of patients respond to the treatment. The use of enriched-design studies often makes the proportion of responders appear larger than it really is. As with nootropics, longer durations of therapy improve the chances of evoking demonstrable effects. The psychometric scales and tests employed were in most cases not comparable with those used in the nootropic trials. In the few studies in which comparable scales and tests (MMSE, ADL) were used, the effects observed were of roughly the same magnitude as those produced by the nootropics. Although the methodology was much more nearly uniform than in the nootropics studies, there was no test that yielded consistently positive results in all trials.

V. PRECLINICAL EFFECTS OF THE NOOTROPICS IN THE LIGHT OF CLINICAL FINDINGS

Before considering the extent to which the clinical data meet the expectations based on preclinical findings, I must stress once again that the clinical investigations were exclusively aimed at showing whether or not the preparations exerted any therapeutic effects. For that reason a wide battery of tests was used, comprising both behavioral aspects and cognitive performance. The somewhat unfortunate efforts of many authors to make use of data from animal experiments in explaining the rationale of their studies and discussing the clinical results should not be allowed to obscure the fact that neither were the studies designed to validate the preclinical results, nor were the clinical results in any way adjusted to serve that purpose.

In the vast majority of the preclinical studies, a design was used in which the experimental animals were exposed to the learning situation while under the influence of the drugs and then tested for retention 24 hours later, either still, or no longer, under the influence of the drugs. In the clinical studies, however, retention performance was tested after short-term intervals, i.e., either

immediately after acquisition or after a lapse of 10 minutes. The several hours' delay preceding the emergence of detectable memory-facilitating effects that has been observed in the most recent animal experiments[4,24] strongly emphasizes the crucial importance of allowing long enough retention intervals, provided only, of course, that the clinical effect and the memory facilitation observed in animals come about by way of the same mechanism. What the long-term memory tests used in the clinical studies detected was not the influence of the substances on long-term storage, but their influence on retrieval from LTM, i.e., on the recall of information acquired while not under the influence of the drugs. Often, learning capacity was tested before and at the end of the treatment period: i.e., performance without the influence of the drugs was then compared with performance while under the acute influence of the drugs. There is thus still no sound scientific evidence of the predictive validity of the animal procedures. This aspect should be examined in specifically designed clinical investigations.

The various reports nevertheless do contain at least a few allusive remarks consistent with the expectations based on animal experiments. In the study with oxiracetam by Dager et al.,[59] for example, there is a sentence reading: "although long term recall improved only negligibly, his long term memory storage (learning capacity) and recognition memory were moderately enhanced." Similarly McLean et al.[56] state that: "The most dramatic demonstration of improvement with pramiracetam ... occurred in the selective reminding test-delayed recall, long term memory retrieval and long term storage." Last, but not least, there are a number of reports concerning the effects of piracetam in dyslexic children that possibly point to effects on LTM storage. In a double-blind, placebo-controlled study by Wilsher et al.[52] the children showed greater facility in reading and comprehension after a 36-week phase of treatment with piracetam. It is very probable that the improved performance at the end of the treatment period reflects, not an acute effect on memory retrieval, but rather an improved availability of the knowledge acquired throughout the duration of treatment, i.e., long-term retention of information acquired under the influence of piracetam. This view is strongly supported by the fact that the combination of psychological training and nootropic therapy proved particularly effective, not only in dyslexic children, but also in other forms of cognitive underperformance.[33] Moreover, it appears very likely that the effects observed after long-term treatment of Alzheimer patients might, at least partially, be based on such effects, too.

However, the many reports on an improvement in noncognitive aspects in individual studies or patients make it seem improbable that nootropics act exclusively on LTM storage. It is conceivable that the effect comes about via a modification of general processes that play an important role in the performance of brain cells. The improvement in long-term storage would then be only one of the measurable consequences. The reason for the usually modest extent of the clinical effects could be that the action of the substances is confined to cells that are still functionally competent. But since the individual patient's specific pattern of functional deficits reflects the impairment of the neuronal circuits essential to this function, it may be that the aspect most unpaired through degeneration also affords the least room for improvement. This applies equally to cognitive and noncognitive performances. It is therefore perfectly conceivable that while measurable effects in one aspect or another may be detectable in a wide-ranging psychometric investigation, these aspects may be of little therapeutic relevance to the symptoms that are particularly disabling for the patient.

VI. SYNTHESIS AND OUTLOOK

Given the observed overall positive effects of the nootropics and their occasionally quite distinct effects in individual patients, this category of compounds would appear useful. The results available so far give no indication that tacrine is superior to the nootropics, or vice versa. The effects of these drugs seem to be similar, although the complication that the double-blind nature in connection with cholinomimetics is very probably wishful thinking (dicriminative stimulus properties,[34] side effects, e.g., reference 74) has been completely left out of consideration. In the absence of comparative studies, the tacit assump-

tion that the cholinomimetics are more effective most likely reflects the superficial plausibility of the underlying hypothesis rather than the existing clinical results. Together, the clinical results present a mirror image of the preclinical profile.

In order to maximally exploit the available therapeutic possibilities, it would be desirable to give priority to the characterization of a subgroup of patients likely to respond to a particular therapy. The steroid dependence of the memory-facilitating effect of the nootropics[23,31] opens up a practical possibility in view of the fact that a very large percentage of Alzheimer patients have elevated plasma cortisol concentrations.[85] This approach would, of course, be valid only if the memory-enhancing effects seen in preclinical studies and the effect observed in patients come about by way of the same mechanism. This brings us back to the question of the validity of the preclinical models, which urgently need clarifying by clinical trials specifically designed for that purpose.

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ALUATION OF THE EFFICACY OF PIRACETAM IN TREATING INFORMATION ROCESSING, READING AND WRITING DISORDERS IN DYSLEXIC CHILDREN

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Piracetam, a new class of drug (nootropil) thought to enhance specific cognitive skills, was given in a 3300 mg daily dose to half of roup of fifty-five dyslexic boys aged 8–13 years, in a 12-week, double-blind, placebo-controlled study. The other half of the subjects eived placebo. All subjects met the following criteria: normal intelligence, normal educational opportunities, no severe emotional blems, no neurological handicaps, good physical health, not taking other psychotropic medication, and scoring at least one and one f below their mental age equivalent on the Gilmore Oral Reading Test. Non-verbal (auditory and visual) and verbal ce and memory skills were examined, and reading, spelling, language and writing abilities were measured using standardized truments. Compared to the placebo control group, individuals treated with Piracetam did not show statistically significant provements above their baseline scores on measures of perception, memory, language, reading accuracy or comprehension, or ting accuracy. However, reading speed and numbers of words written in a timed period were significantly enhanced in subjects ated with Piracetam as compared to placebo. Effective reading and writing ability, taking both rate and accuracy into sideration, were also significantly improved in the Piracetam as compared to the placebo treatment group. The medication was l-tolerated and medical examinations showed no significant adverse reactions. These results encourage further study of Piracetam determine more precisely the mechanism of action by which specific cognitive skills are affected.

TRODUCTION

Recent reviews of chemotherapeutic treatment learning disabilities have emphasized that the rceptual and behavioral changes induced by ugs do not necessarily lead to improved academic rformance (Aman, 1980; Werry, 1981). This nclusion has been based primarily on research th central nervous system stimulants such as ethylphenidate (Ritalin) and dextroamphetamine lexedrine). Such stimulants have been shown to prove attention span (Barkley, 1977; Barkley d Jackson, 1977), memory (Sprague, 1972; Werry and Aman, 1975), and impulsivity and social behavior (Barkley and Cunningham, 1980; Conners and Werry, 1979). However, studies of educational abilities using standardized reading, spelling and arithmetic tests have failed to demonstrate any significant differences in the performance of treated children (Quinn and Rapoport, 1975; Weiss et al., 1975) or non-hyperactive children (Gittleman-Klein and Klein, 1976; Aman and Werry, 1982).

This discrepancy between the drug-induced improvements in behavioral control and the absence of change in school-performance may be due in part to the way each child is assigned the proper dosage. In the past, clinicians and investigators have assumed that the optimal dosage to improve

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behavior would coincide with the levels of drug needed for improved learning. Gittleman-Klein and Klein (1975) demonstrated, however, that there was no association between improvements in behavior and increases on academic test scores among children treated with Ritalin. Sprague and Sleator (1977) have proposed an inverted U-shaped functional relationship between the medication dosage and performance on cognitive or behavioral tasks. There is a zone of peak-enhancement or actual deterioration of the performance. Their studies have suggested that zones of peak-enhancement are not the same for cognitive and behavioral tasks. The optimal zone for social tasks requires a slightly higher dosage than the optimal zone for cognitive tasks. Thus, the best dosage for cognitive tasks appears to be too low to enhance social functioning, whereas the optimal zone for social enhancement is too high a dosage for improving cognitive skills. Since stimulants are usually prescribed for improving social behavior, children taking these medications may be receiving dosages that are too high for enhancing cognitive skills.

To avoid the ambiguities of such dosage-dependent effects, many investigators have focused their efforts on the study of cognitive effects due to psychotropic medications. Recent attention has been given to a new class of psychoactive drugs called nootropils. Piracetam, a nootropic substance, has been studied for its facilitation of learning and memory consolidation (UCB, 1980). Chemically, Piracetam (2-oxo-pyrrolidine-acetamide) shows a kinship to γ-aminobutyric acid GABA and appears to have no stimulating or sedating effects (Stegink, 1972; Calliauw and Marchau, 1975). Dimond (1975) and Dimond and Brouwers (1976) report that Piracetam increased verbal learning and improved performance on coding and short-term memory tasks with normal adult subjects. Other researchers have also noted that Piracetam significantly enhances performance on a variety of tasks which assessed presumed left-hemispheric functioning (Squitieri et al., 1975; Mindus et al., 1976). As such, Piracetam may be a particularly appropriate drug for treating children with some forms of learning disabilities including dyslexia since many such children have been shown to have relatively poor perceptual and short-term memory abilities (Rudel and Denckla, 1974; Tallal, 1980a; Tallal, 1980b) and poor coding and naming abilities (Symmes and Rapoport, 1972; Denckla and Rudel, 1976).

Three studies have tested the effects of Piracetam on learning-disabled populations. The first study reported was by Wilsher et al. (1979), who used adult dyslexics as subjects. In this study, 16 adult dyslexics were matched on the basis of their WAIS IQ scores with 14 control subjects for a 3-week placebo-controlled, double-blind, crossover trial of 4800 mg daily dose of Piracetam. The dyslexic subjects met the criteria outlined by Thomson (1977). Since subjects in this study demonstrated significant carryover effects due to the crossover design, Wilsher et al. only examined results from the first period of treatment to avoid the confounding effects from previous exposure to Piracetam. In comparison to placebo treatment, results showed that in the dyslexic group who received Piracetam verbal learning improved by almost twice that of the non-dyslexic control group receiving Piracetam (15% compared to 8.6%). The test used was a serial memory verbal learning task with 10 three-letter nonsense syllables. In addition, the number of instances that a subject learned the nonsense syllable and then forgot it on the very next trial dropped by almost half among the dyslexic group treated with Piracetam (−47.1%), but was not changed in the dyslexic placebo treatment group.

Simeon et al. (1980) were the first to test the efficacy of Piracetam on learning skills of children. They treated 29 'learning disordered' boys between the ages of 8 and 14 with a 4800 mg daily dose of Piracetam in a double-blind, crossover placebo-controlled 4-week study. All children were at least one year behind their age group in either reading, spelling or arithmetic on the Wide Range Achievement Test (WRAT) and all had a Full Scale WISC-R IQ of at least 85. Their findings on measures of global behavior and learning were non-significant, although the author points out that the short duration of treatment, carryover effects due to the crossover design, and the small number of patients in various treatment subgroups made statistical analyses difficult to interpret.

In a second study by Wilsher et al. (1985), 46

dyslexic boys aged 8 to 13 years were treated in an 8-week, double-blind, placebo-controlled trial of 3300 mg daily of Piracetam. All subjects met the following criteria: they had a Full Scale WISC-R IQ greater than 90, a Reading or Spelling Age of at least two years behind their mental age based on the WISC-R, normal educational opportunities, no severe emotional problems, normal hearing and normal vision, and no gross neurological deficits. The children were tested on their reading ability (speed, accuracy, and comprehension) and a 5-min free-writing sample was taken to measure the total number of words written and the percentage of spelling mistakes. *T*-test comparisons between the means of the two treatment groups at the beginning and the end of the 8 weeks showed no significant differences on any of the dependent measures. However, further analysis comparing the mean treatment changes from baseline, using the difference between the post- and pretreatment scores for each subject, revealed improvements in reading speed and accuracy and total words written for individuals treated with Piracetam. In all 3 studies, the Piracetam medication was extremely well-tolerated.

The present study was designed to replicate and extend the findings of Wilsher et al. (1984). More rigorous patient-selection inclusion and exclusionary criteria were used. Drug dosage and regimen were equivalent, but the clinical trial was extended to 12 weeks and additional subjects, test sites, and psychometric tests were included.

METHODS

Subjects

Six different centers participated in the study. At our site in San Diego, 61 developmentally reading-disabled children were studied over a one and a half year-period, from the spring of 1981 to the summer of 1982. All children attended school during the course of the study and met the following criteria. (1) They were male and between the ages of 8 years, 0 months and 13 years, 11 months old at the initial visits. (2) They had a Full Scale IQ score of 80 or more on the Wechsler Intelligence Scale for Children-Revised (WISC-R) or in a Performance Scale IQ or a Verbal Scale IQ of 90 or more, obtained within 9 months of the initial visit. (3) They had a Reading Quotient of less than or equal to 0.85. (4) English was their primary language. (5) Informed consent was obtained from both patient and parent or legal guardian. (6) They had normal audiological and ophthalmological functioning. (7) There was no significant neurological handicap. (8) They had no severe emotional disturbance as a primary symptom. (9) There was no severe educational deprivation. (10) They had no clinically significant laboratory abnormalities, nor any medical conditions which might put the patient at additional risk or interfere with the conduct of the study. (11) They had no history of significant adverse reaction or hypersensitivity to Piracetam. (12) They were not involved in any therapies which might interfere with the evaluation of efficacy and safety, including: psychostimulant medication within 6 months of the initial visit, concomitant drug therapy with psychostimulants or any drug for emotional disturbance, concomitant therapy with Tofranil for any indication, investigational drug therapy within one month of the initial visit, or concomitant chronic treatment with bronchodilators which have central stimulant activity.

The Reading Quotient was calculated as equal to: Reading Age × 100% by Chronological Age × Full Scale WISC-R IQ. The Reading Age was derived from the Accuracy Score of the Gilmore Oral Reading Test — Form C. Grade Scores from the Gilmore were converted to Age Scores using Table II provided in the Gates-McKillop Oral Reading Test. Abnormal audiological functioning was defined as a loss of greater than 20 dB in either ear for two frequencies in the normal range (500, 1000, 2000, 3000, 4000 Hz, using pure tones). Abnormal ophthalmological functioning was defined as less than 20/40 corrected vision in both eyes as tested by the American Optical E Chart. Significant neurological handicaps were defined as any of the following: acquired neurological disease, classical neurological signs with functional impairment or seizures within the last 5 years. The patients had not received anticonvulsant therapy for at least two years prior to the initial visit. Educational and emotional evaluations were made

by the medical staff following usual clinical practice. Four subjects were dropped from the study: one moved, one suffered from an asthma attack and was treated with bronchodilators (in violation with the protocol) and two were removed from the study due to medical complications unrelated to study medication (both were taking placebo). The fact that a child was currently receiving academic remedial assistance or had received such tutoring in the past did not preclude entry into the study.

Procedures

Placebo and Piracetam treatments were randomly divided among 6 groups of 10 subjects, each on a double-blind basis with the restriction that there be equal numbers of each treatment within each of the 6 groups. Patients were then assigned to one of the 6 groups on the basis of their age; that is, 8-year-olds were assigned to Group One, 9 years olds to Group Two, and so forth. When all the treatment medication had been used up within a group, the patient was assigned to the group with the fewest members. Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml, administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed.

The study consisted of 5 visits. An initial screening visit usually occurred one week prior to the start of treatment. The treatment period was 12 weeks long, with follow-up visits after 2 weeks, 6 weeks, and 12 weeks of treatment. At week 4 and week 9, the patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

At the initial screening, patients were tested to determine their eligibility. Hearing and visual acuity tests were given, a developmental history taken, IQ testing was done as needed, and the Gilmore Oral Reading Test was also administered to provide a calculation of the Reading Quotient. Assessment of education experience and emotional health was also performed at this time.

A complete physical examination was performed by a physician at the second or induction visit and again at the last visit. A medical history was taken during the second visit and abbreviated physical examinations were performed at the second and sixth week visits. Observations for possible adverse effects and assessment of general health were emphasized. Laboratory evaluations were obtained at the induction visit, the 6-week, and the 12-week visits. The laboratory tests included hematology, urinalysis and blood chemistry to test for possible adverse side-effects.

Tests

All 6 study centers followed the same protocol and used a common battery of tests to measure drug efficacy. In addition, each site conducted additional 'special studies'. Only the results from the common test battery and special study conducted at the San Diego site are reported in this paper. The common test battery was administered at the induction and final (week 12) visits, while the special study tests were given at the induction and week 6 visit. At the San Diego Center, all testing for an individual patient was administered by the same tester and took approximately 1½ h. These tests included: the Gilmore Oral Reading Test — Form C at the initial visit and Form D at the final visit —, Information for Reading Accuracy, Comprehension and Rate were included; the Digit Span subtest of the WISC-R, both digits forwards and backwards administered via a tape recording; the Gates-McKillop Syllabication subtest — Form 1 at the induction and Form 2 at the 12-week visit; the Wide Range Achievement subtest for Spelling; a 5-min free-writing sample was taken to include the total number of words, number of words misspelled and the number of occurrences of the most frequently written word; the Rapid Automatized Naming Test (Denckla and Rudel, 1976); a behavioral assessment in the testing situation made at the induction and 12-week visits on a rating scale of 1 to 4 (1 being excellent, 4 being poor), measuring distractibility from following instructions, social appropriateness, cooperativeness, attention and general motor activity; and a parent's global assessment of the child's behavior obtained at the 12-week visit on a rating scale of 1–5, where 1 is much improved and 5 is much worse, considering their behavior at home, interaction with peers and school reports concern-

ɜ behavior and performance in evaluating the ange from the start of the study.

In addition to these common tests, we con- cted additional special studies. Subjects were en the Repetition Test, developed by Tallal)80), with 3 sets of stimuli: (1) non-verbal audi- y tones (75 ms duration), differing in funda- ntal frequency; (2) non-verbal visual nonsense apes (75 ms duration); and (3) auditory stop- nsonant vowel syllables (ba/da) with 40 ms ration formant transitions. The Repetition Test s been shown to be a highly sensitive measure of ceptual and memory functioning. In addition, s theoretically based on a model of perception d is comprised of a series of substests designed assess levels of perception and memory in a rarchical manner (see Tallal, 1980, for a detailed scription of these procedures). Four dependent asures were made on each of the 3 versions of Repetition Test. Subjects were scored for the al number of correct trials, the number of cor- t using interstimulus intervals (ISI's) of) n. ne number of trials using ISI's less than) ms and the number of trials needed to reach terion. Improvements in trials to criterion scored icate an increased rate of learning stimulus–re- nse associations. Increases in scores on trials h short ISI's suggest an improvement in rate of cessing and temporal sequencing abilities. provements in the longer ISI scores suggest an rease in short-term and serial memory.

In addition to these experimental perceptual l memory tests, subjects were also given the ken Test (DeRenzi and Vignolo, 1962) to assess eptive language comprehension skills and a red associate visual memory test designed for s study. In the visual memory test the tester tructed the child by saying, 'I would like to see s well you can remember different pairs of tures. I will show you two pictures, one after other. Try to remember them as a pair that go ether'. Testing took place in two parts, a learn- and a recall section. During the learning sec- n, children were presented with pairs of pictures anged as a set. Children were presented with s of 2, 4, 6 and then 8 pairs. If a child success- v led all pairs within a set, they moved to ne higher set and were tested. If any failure occurred, the final testing took place using the next lowest set; e.g., failure on set 6, final testing on set 5. During the learning portion, children were presented with pairs of pictures, one after the other, until the set was completed. Each pair was presented for 3 s with an intertrial interval of two seconds. After all of the pictures in a set had been presented, the child's recall abilities were tested in the following way: the second picture of each pair was grouped, mixed and then laid down on the table in front of the child. Using the same order as presented in the learning portion of the test, the first picture of each pair was presented to the child, and he was asked to find the picture that goes with it among the pictures laid down on the table in front of him. This procedure was continued until all pictures had been matched. Children were scrored for the total number of correctly matched pictures. Improvements on this test suggest increases in visual learning and recall.

RESULTS

From the initial sample of 61 children, 57 successfully completed the study. From this group, two children had poor compliance during the last 6 weeks of the clincial trial period (below 70% as measured from the remaining bottled medication). Consequently, they were removed from the data analysis leaving 55 children, 28 from the piracetam treatment group and 27 in the placebo treatment group.

Table I presents the demographic and baseline characteristics of the Piracetam and placebo treatment groups. *T*-test and χ^2 comparisons between the two groups showed no significant demographic differences. Note that a high percentage of the children were actively receiving remedial tutoring for their reading problems (ca. 70%).

Table II shows the baseline scores for the Piracetam- and placebo-treated groups on the common test battery. Note that the Gilmore Oral Reading test was scored in two ways. First, individual reading ability for accuracy, comprehension and rate was scored. Second, because by reading more slowly, accuracy and comprehension may be improved or vice versa, composite reading scores

TABLE I

Demographic and baseline characteristics

Patient characteristic	*Piracetam (n = 28)*	*Placebo (n = 27)*	*P*
Age, years			
Mean	11.1	11.4	$t = -0.05$ n.s.
S.D.	1.9	1.6	
WISC-R, VSIQ			
Mean	97.8	98.0	$t = -0.1$ n.s.
S.D.	10.9	10.8	
WISC-R, PSIQ			
Mean	107.2	107.1	$t = 0.0$ n.s.
S.D.	11.2	12.1	
WISC-R, FSIQ			
Mean	102.4	102.5	$t = -0.1$ n.s.
S.D.	9.6	11.2	
Reading quotient			
Mean	0.73	0.72	$t = 0.9$ n.s.
S.D.	0.07	0.07	
Reading class			
Tutoring	20	20	$\chi^2 = 0.0$ n.s.
No tutoring	8	7	
Relatives			
Dyslexic	18	21	$\chi^2 = 0.5$ n.s.
Non-dyslexic	10	6	

n.s. = not significant, $P > 0.05$.

were calculated to reflect the interaction between reading speed, and reading accuracy and comprehension. A composite score for 'effective reading accuracy' was calculated by multiplying the percentage of words read correctly by the reading rate. Similarly, 'effective reading comprehension' scores were calculated by multiplying the percentage of correctly answered comprehension questions by the reading rate (Jackson, 1980). Scores are multiplied rather than added together, because they use different units of measurement. Composite reading scores are always a positive number and reflect a child's total reading effort.

T-test comparisons between groups at baseline showed non-significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group at baseline on the percentage of spelling errors in the free-writing test ($t = 2.64$, $P < 0.01$). There were no other significant baseline differences between groups on the common test battery.

Table III gives the baseline scores for the Piracetam- and placebo-treated groups on the experimental test battery. *T*-test comparisons between groups at baseline again showed no significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group on the Paired Associate Visual Memory Test at baseline ($t = 2.0$, $P < 0.05$). There were no other baseline differences on the experimental test battery.

To assess the effect of drug treatment, the mean change from baseline was calculated for each subject on each measure and then averaged and compared for each treatment group.

Table IV shows the mean change from baseline (posttest–pretest scores) for each measure in the common test battery for the Piracetam and placebo groups. As seen in Fig. 1 for individual reading scores, the Piracetam group demonstrated a statistically significant improvement over the placebo group (at the $P < 0.003$ level of accuracy) on their reading rate from the Gilmore test. The Piracetam group increased their reading speed by almost 8 words per min (−10%) whereas the placebo group decreased by 3 words per min (−4%), leaving a difference of almost 11 words per min between the

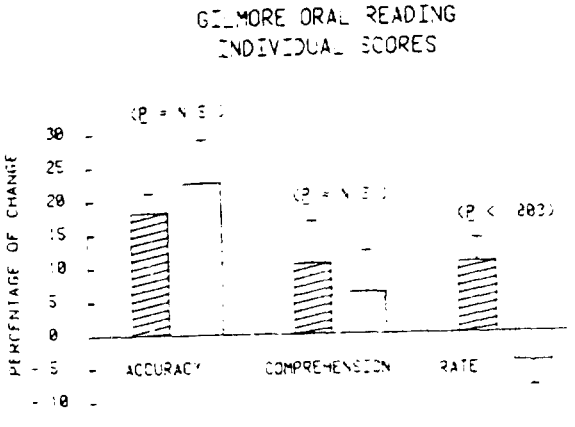


Fig. 1. Percentage of change from baseline (posttest minus pretest scores) made by the Piracetam and placebo treatment groups are shown for the accuracy, comprehension and rate scores of the Gilmore Oral Reading Test.

ABLE II

seline scores for the Piracetam and placebo groups on the common test battery

st name	*Piracetam*	*Placebo*	*t-test*
lmore oral reading			
Accuracy (grade rating)	3.3	3.1	n.s.
Reading comprehension (grade rating)	4.8	4.9	n.s.
ading rate (words min)	76.9	77.6	n.s.
lmore composite reading (% correct × rate)			
Accuracy	6 774.3	6 883.9	n.s.
Comprehension	6 646.3	6 683.3	n.s.
git span (scaled score)	7.2	7.2	n.s.
ites-McKillop syllabication raw score)	11.6	12.1	n.s.
ords written (total)	41.0	44.1	n.s.
rcent of spelling errors [b]	21.5	12.3	$P < 0.01$ [a]
n color [b]	42.3	46.7	n.s.
n number [b]	31.4	35.0	n.s.
n [b]	32.4	37.1	n.s.
n object [b]	61.3	65.0	n.s.

ne-tailed test of significance. [b] reduction in score indicates improvement

ABLE III

seline scores for the Piracetam and placebo groups on the perimental test battery

st name	*Piracetam*	*Placebo*	*t-test*
on-verbal — ual test			
Long ISI's	23.4	23.4	n.s.
Short ISI's	10.9	11.5	n.s.
petition test — lables			
Long ISI's	13.5	12.7	n.s.
Short ISI's	7.1	6.8	n.s.
petition test — n-verbal auditory			
Long ISI's	19.2	21.4	n.s.
Short ISI's	11.3	13.1	n.s.
ired associate Memory test	18.0	24.5	$P < 0.05$ [a]
[illegible]			
[illegible]	[illegible]	[illegible]	n.s.
[illegible]	[illegible]	[illegible]	n.s.

[a] One-tailed test of significance

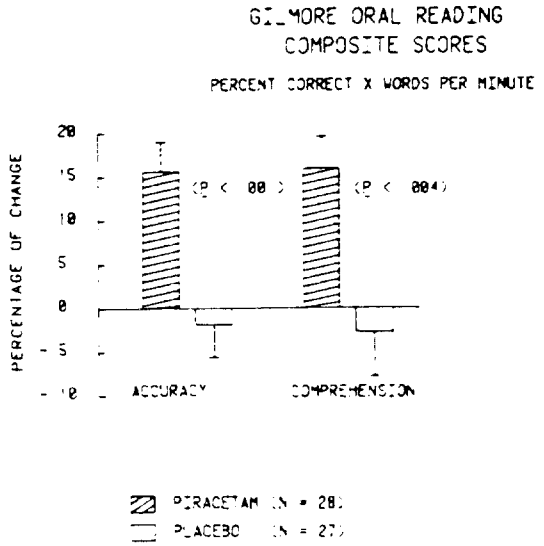


Fig. 2. The Composite Reading scores, derived by multiplying the percentage correct by the number of words read per min. on the Gilmore Oral Reading test are shown for the Piracetam and placebo treatment groups. Percentage change from baseline (posttest minus pretest composite scores) are shown separately for accuracy and comprehension.

TABLE IV

Mean change from baseline score for the Piracetam and placebo groups on the common test battery

Test name	*Mean change from base-line (post- pretest score)*				
	Piracetam	*Placebo*	*t*	*d.f.*	*P* [a]
Gilmore oral reading					
Accuracy (grade rating)	0.6	0.7	−0.55	53	0.29
Reading comprehension (grade rating)	0.5	0.3	0.40	53	0.34
Reading rate (words/min)	8.0	−3.4	2.39	53	0.003
Gilmore composite reading (% correct × rate)					
Accuracy	1055.6	−132.1	3.43	53	0.001
Comprehension	1054.0	−189.7	2.98	53	0.003
Digit span (scaled score)	0.9	0.3	1.03	53	0.15
Gates-McKillop syllabication (raw score)	2.2	2.9	−0.83	53	0.21
Wrat spelling (grade rating)	0.2	0.3	−0.49	53	0.31
Words written (total)	6.1	2.2	1.08	51	0.14
Percent of spelling errors [b]	−4.1	7.4	−2.51	51	0.008
Ran color [b]	−1.9	−1.3	−0.30	53	0.38
Ran number [b]	−1.6	−2.5	0.70	53	0.24
Ran letter [b]	−2.1	−3.1	0.55	53	0.29
Ran object [b]	−3.4	−1.3	−0.73	53	0.24

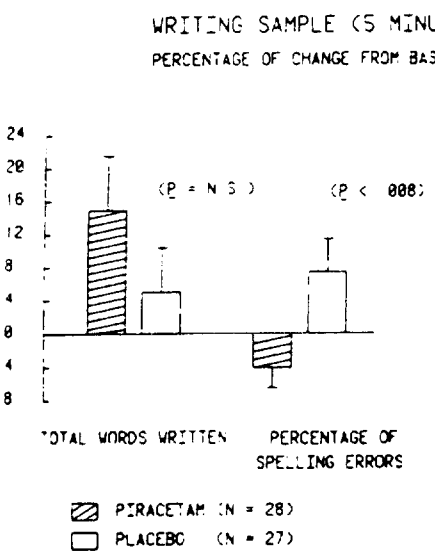
[a] A one-tailed test of significance. [b] reduction in score indicates improvement.

two groups. This increase in reading speed for the Piracetam group was accompanied by improved reading accuracy and comprehension, although similar gains were also found in the placebo group and, thus, cannot be ascribed to drug effect. There were no significant differences between groups on reading accuracy or comprehension.

Composite reading test scores shown in Fig. 2 demonstrate that the Piracetam group significantly improved their effective reading by 16% during the course of the study, on both their effective reading accuracy and comprehension scores, whereas the placebo group decreased on both composite reading scores. This difference in performance between the two treatment groups was highly significant (effective reading accuracy, $t = 3.43$, $P < 0.001$; effective reading comprehension, $t = 2.98$, $P < 0.004$).

A comparison of composite and individual reading scores reveals that although the placebo group did increase in their reading accuracy and comprehension this was accomplished at the expense of their reading speed which decreased, producing very little effective change in their overall reading performance. The Piracetam group, on the other hand, not only improved their reading accuracy and comprehension but also simultaneously was able to increase their reading rate. This resulted in significant gains in their overall reading performance.

Fig. 3 shows that on the Free-Writing Test, both groups showed an increase in the total number of words written. The Piracetam group improved 15% whereas the placebo group showed only a 5% gain, although this difference was not statistically significant. The Piracetam group, how-



3. Percentage of change from baseline (posttest minus test scores) made by the Piracetam and placebo treatment ups are shown for the 5-min free-writing sample. The total nber of words written in 5 min by each treatment group, as l as the percentage of spelling errors are graphed.

r, did show significant improvement over the cebo group in the accuracy of their spelling < 0.008). The Piracetam group decreased the centage of spelling errors (number of errors/ al words written) by 4% whereas the placebo up increased in spelling errors by over 7%. ese figures change, however, if one placebo 'out-' subject, who scored well above the rest of the up (83%), is removed from the analysis. Then placebo group shows only a 4.5% increase in lling errors ($P < 0.02$). Nevertheless, the trends nain the same. Overall, the Piracetam group not ly increased in their writing speed, but also proved in their spelling accuracy. The placebo up's increase in writing speed, however, was set by additional spelling errors.

Analysis of the mean change from baseline retest–posttest scores) for each measure in the perimental test battery for the Piracetam and cebo groups showed that there were no signifi- nt differences found between treatment groups any of the experimental perceptual, memory or nguage measures given.

P s from laboratory evaluations of blood er hematology and urinalysis were consistent with previous findings, showing no significant medical abnormalities among the Piracetam-treated subjects. The double-blind rating of drug tolerance by the physician indicated that Piracetam was well-tolerated by the children (mean rating = 1.1 (± 0.1), 1 excellent, 4 poor). Except for the one child who suffered from an asthma attack, all the children who were treated with Piracetam remained healthy.

DISCUSSION

These results confirm some of the previous findings of Wilsher et al. (1984) that Piracetam increases the rate of reading and of writing accuracy. The amount of changes found in this present study are comparable to the results obtained by Wilsher. In Wilsher's 8-week study, subjects improved their reading rate by 5%. The amount of change found in the present 12-week study is proportional to Wilsher's data with a 10% improvement in reading rate. This finding, seen in the light of Wilsher's previous data, suggests that the degree of Piracetam-induced improvement in reading and writing may be related to the duration of treatment. However, improvement over time was not assessed directly in the present study. Additional studies will be necessary to establish the effects of dose-duration.

The present study failed to confirm Wilsher's previous findings of drug-improved reading accuracy. The lack of improvement may be due in part to some very large placebo responders; in fact, the largest improvement in reading accuracy (79%) was found in a member of the placebo group.

Substantial changes in reading accuracy and comprehension ability occurred over the course of the study for many of the dyslexic children in both the Piracetam- and placebo-treated groups. This was somewhat unexpected as the reading skills of dyslexic children as a group are known to be difficult to remediate. These marked changes in reading suggest that perhaps the attention and positive reinforcement given to the children in the study, together with the expressed goal of helping them improve their reading skill by using a unique method, a medication, added to the improvement

made. It is of considerable interest that the improvements noted in the placebo-treated group mirror the instructions given to them on reading and writing tests.

On the Gilmore reading test children were told to read the passages as well as they could. Although the children on placebo did improve their reading accuracy and comprehension, as instructed to do, they did so by slowing down their rate of reading (over their baseline reading rate) to achieve this improvement. Thus, they had to lose ground in rate in order to gain it in accuracy and comprehension. The dyslexics on Piracetam, on the other hand, did not need to resort to this strategy to achieve improvement in reading accuracy and comprehension. Rather, they were able to significantly increase their reading rate as well as their accuracy and comprehension over their original baseline performance. That is, they did not have to lose ground in order to gain ground. They gained both speed and improved accuracy and comprehension over the course of the study. The percentages of subjects in the Piracetam and placebo treatment groups showing gains and losses in reading accuracy and rate are shown in Fig. 4.

On the writing sample subjects were told to write as much as they could during a specified time-period. The placebo-treated children did just that. They increased the number of words written over their original baseline performance. However, as was found in reading, they made this gain at the expense of something else, in this case an increased number of spelling errors. The dyslexics on Piracetam did not show this 'lose-to-gain' pattern. Rather, they increased both the number of words written as well as decreasing the number of spelling errors they made. Even though the only significant difference between groups noted at baseline was the number of spelling errors made, with the Piracetam group making more errors than the placebo group, by the end of the study this order was reversed. The Piracetam group made fewer spelling errors than the placebo group.

Some of the measures in the special perceptual, memory and receptive language studies suffered from ceiling effects, as most of the subjects found these tests to be relatively easy, indicating adequate perceptual, memory and language abilities for their age. Most of the subjects performed at the top of the scale on all subtests of the Repetition Test as well as on all 5 parts of the Token Test, indicating normal perception and receptive language abilities at the onset of the study, hence leaving little room for improvement. Only 4 subjects scored at least one standard deviation below the mean on the Token Test, suggesting that Mattis et al.'s (1975) language disorder syndrome was poorly represented in this dyslexic sample. Subjects also scored highly on perceptual subtests of all 3 Repetition Tests, indicating that they had no difficulty in discriminating between the different auditory or visual stimuli. A subgroup of 19 subjects did have difficulty discriminating between the two computer-synthesized speech syllables /ba/ and /da/ with 40 ms formant transitions. On the Repetition Test however, perhaps due to the very small sample size, a χ^2-test indicated no significant differences between Piracetam and placebo groups on this test. Contrary to previous findings (Dimond, 1975; Wilsher et al., 1979), subjects taking Piracetam did not demonstrate statistically significant improvements in their short-term and serial memory skills, although some differences between non-verbal and verbal stimuli were found.

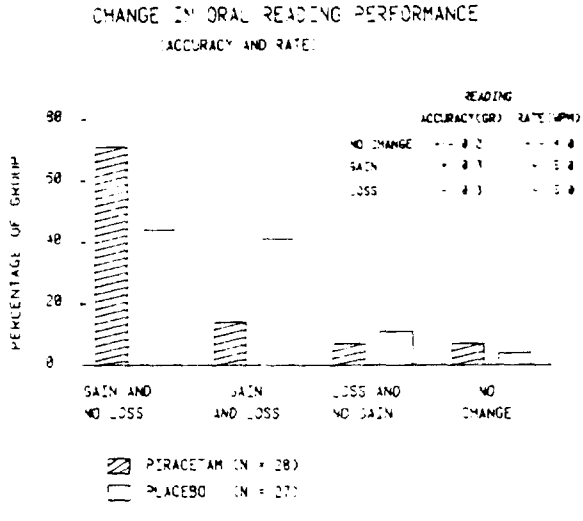
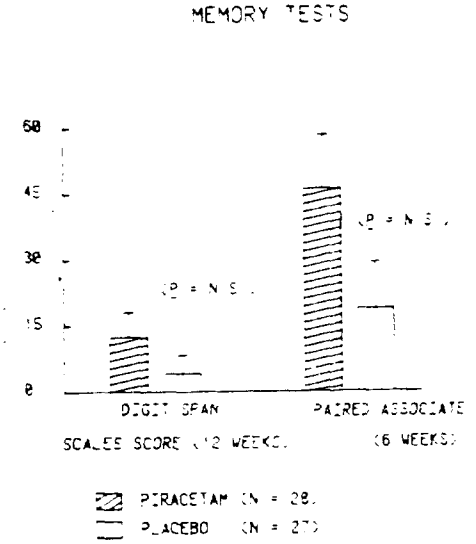


Fig. 4. Composite reading scores, derived by multiplying reading accuracy by rate (words read per min), on the Gilmore Oral Reading test are graphed to show the percentage of the Piracetam and placebo treatment group who made gains and losses in effective reading ability over the course of the study.

sing non-verbal stimuli, treatment groups showed
) significant differences on the total number of
rrect stimulus series recalled in the auditory
odality of the Repetition Test. In the visual
odality, subjects on placebo found it easier to
call the proper sequence of the visual nonsense-
aped stimuli, as demonstrated by their improved
ores for total correct trials with long ISI's. In
ntrast, when test items could be verbally re-
arsed, as in the Paired Associate Visual Memory
st, which used namable pictures as stimuli, and
e Digit Span subtests, the Piracetam-treated
oup's mean final performance and change from
seline was almost twice that of the placebo
oup on both tests (Fig. 5). The difference be-
een groups, however, was not statistically sig-
ficant in either case. These trends toward im-
oved memory for verbally mediated material
ggest that a significant improvement in verbal
emory scores might be realized with a larger
mple size, a longer duration drug trial, or more
ns[illegible] measures. In addition, Piracetam's effect
n [illegible]ory could be mediated by drug-dosage. A
rger (e.g. 4800 mg/day) dosage might produce
gnificant results, since previous findings used a
osage in this range.



g. 5. The percentage of change from baseline (posttest minus retest scores) made by the Piracetam and placebo treatment [illegible]n two verbal memory tests, digit span and paired [illegible] are shown.

This pattern of results calls for a much closer examination of the different stages of memory that may be affected by Piracetam. Future studies should examine possible material-specific effects of Piracetam on various memory components, such as working capacity, rehearsal strategies, retrieval, retention and recall. In addition, the questions of dosage-dependent memory effects should be investigated.

Subject selection procedures may also have important implications for drug studies with dyslexic children. Several different subgroups of reading- or language-impaired children, exhibiting different profiles in the areas of perceptual, memory and language functions, have been described (see Tallal and Stark, 1982, for review). Baseline test scores suggest that the majority of reading-impaired children participating in this study did not have significant perceptual, memory or receptive language deficits associated with their reading disability. Thus, it was difficult to assess the potential therapeutic efficacy of Piracetam in treating such deficits in the present study. In order to better assess Piracetam's ability to effect perceptual, memory or receptive language deficits, it will be important to select a group of reading- or language-impaired children who show significant deficits in these areas at baseline testing. Comparisons between different subgroups of reading-impaired children, selected on the basis of specified behavioral profiles, may be an important factor in assessing the effects of nootropils on learning- and language-impaired children.

In summary, Piracetam appears to improve verbal fluency, as demonstrated by increased rates of reading and writing accuracy. These trends encourage a potential role for Piracetam in the clinical remediation of dyslexia, although questions about drug-dosage, duration of treatment, possible interaction with other remedial procedures, differential effects on various subgroups of learning-impaired children and selectivity of drug-response remain unanswered. Some of these issues are being investigated presently.

One final note of caution — given the number of analyses performed, some of the results obtained could be interpreted as chance occurrences. Selective replication of these findings with a differ-

ent group of dyslexic children is necessary to validate these results.

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The Effects of Nootropics on Memory: New Aspects for Basic Research

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Summary

The mechanism through which nootropics of the piracetam type (i.e., piracetam itself and its analogues oxiracetam, pramiracetam, and aniracetam) improve memory is still uncertain. Its elucidation will, however, not only mark an advance in the treatment of cognitive disorders, but also shed light on the basic processes of memory storage. Although the great majority of the findings available so far seem to suggest cholinergic mechanisms, divergent results are obtained whenever parallel experiments are performed with two or more of these compounds. More recent observations indicate that interactions with steroids take place. All four compounds are inactive in adrenalectomized laboratory animals; chemical blockade of the adrenal cortex with aminoglutethimide and pretreatment wich epoxymexrenon, a potent mineralocorticoid antagonist, eradicated the memory-enhancing effect of all four substances.

Wirkungen der Nootropika auf das Gedächtnis: Neue Aspekte für die Grundlagenforschung

Es besteht noch immer keine Gewißheit darüber, auf welche Weise die Nootropika des Piracetamtyps (Piracetam und dessen Analogverbindungen Oxiracetam, Pramiracetam und Aniracetam) das Gedächtnis verbessern. Die Klärung dieser Frage würde nicht nur einen Fortschritt bei der Behandlung kognitiver Störungen darstellen, sondern auch die der Gedächtnisspeicherung zugrundeliegenden Vorgänge erhellen. Obwohl die große Mehrzahl der bislang verfügbaren Befunde auf cholinergische Mechanismen hinweisen, werden widersprüchliche Ergebnisse erzielt, sobald parallele Experimente mit zwei oder mehreren dieser Verbindungen durchgeführt werden. Neuere Beobachtungen scheinen auf Wechselwirkungen mit Steroiden hinzudeuten: alle vier Verbindungen sind bei adrenalektomierten Labortieren unwirksam; sowohl eine chemische Blockierung der Nebennierenrinde durch Aminoglutethimid als auch eine Vorbehandlung mit Epoxymexrenon (einem potenten Mineralokortikoidantagonisten) blockierte die gedächtnisverbessernde Wirkung aller vier Substanzen.

The elucidation of biochemical bases and the regulation of memory is one of the greatest challenges in neurobiology. It is therefore hardly surprising that every year hundreds of papers are published dealing with some particular facet of memory. Our knowledge of the subject matter increases almost daily, but more in width than in depth. We now know of many transmitters, receptors, and modulators that play some part in memory processing; but each new finding is soon relativized by the realization that it is not generally valid, but simply sometimes true under certain limiting conditions. In this field, progress tends to follow the discovery of a new pharmacological tool, e.g., a new specific receptor blocker or activator, or an enzyme inhibitor. Consequently, the prevalent method in efforts to identify the mechanisms and the neuronal networks operative in memory processing relies on the testing of mechanistically specific preparations for potential effects on memory in animal models. For example, the NMDA blockers (MK 801, AP5, and AP7) that recently became available encouraged studies of the influence of NMDA blockade on learning and memory and speculation about the possible involvement of this type of receptor in memory processing (*Morris* et al., 1986). In the meantime, it has become evident that the responses seen under NMDA blockade only apply in certain circumstances and to certain processes of memory (*Mondadori* et al., 1989). Thus, while the assortment of transmitters involved in memory processing increases, that does nothing to alter the fact that almost every pharmacological manipulation of the CNS has some influence on certain, though not all, forms of learning and memory (*Mondadori*, 1987).

The opposite way of seeking insight into the processes of memory consists in characterizing biochemically the substances known to affect memory, and then attempting to correlate certain components of their biochemical profile with their effect on memory. The memory-blocking effects of certain antibiotics such as puromycin, anisomycin, and cycloheximide, for instance, inspired a very large number of studies of the possible relations between inhibition of protein synthesis – scientifically the most appealing aspect – and memory (for a review see, for example, *Davies* and *Squire*, 1984). The underlying mode of action has, however, always remained conjectural, because these antibiotics exert many other known

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effects (see, for example, *Flexner* and *Goodman*, 1975; *Rainbow* et al., 1979) and quite probably just as many other unknown effects that might equally well be responsible for the disturbance of memory, or at least contribute to it. The possibility that the known biochemical effect under scrutiny may not be responsible for the observed effect on memory, or that that effect may be due to the interplay of several discrete effects, must always be taken into consideration, even in studies using the abovmentioned "specific tools": failure to do so makes false conclusions unavoidable.

One practicable and valid approach to the experimental investigation of mechanisms underlying memory storage, or the regulation of memory storage, may be afforded by the piracetam-like nootropics. These are interesting preparations, above all because they exert distinct, positive effects on various manifestations of memory, yet provoke few or no side-effects. The fact that they have so far been found to display scarcely any effects in most of the traditional assays used in biochemistry laboratories may make them appear all the more or all the less attractive, depending on the viewpoint of the observer. If, however, as has already been suggested (*Giurgea*, 1973, 1982), they do act specifically on cognitive processes or on the structures and mechanisms responsible for cognitive processes, then the elucidation of their mode of action might represent a very significant advance. The following remarks, illustrated by a selection of experimental observations, will be concerned with the progress made to date along this line of research and the possibilities emerging from it.

Neuropharmacological findings

The first experimentally demonstrable effect of piracetam, the prototype substance, on the CNS was inhibition of central nystagmus in the rabbit (*Giurgea* et al., 1967). In retrospect, however, the vast majority of the experimental preclinical findings seem to be indicative of effects on cognitive processes, in particular on learning and memory in a very wide variety of forms. Piracetam, for instance, diminishes the disruptive effect of a cerebral electroshock on the orientation of rats in a water maze (*Giurgea* and *Mouravieff Lesuisse*, 1972). Many other authors have also observed anti-amnestic effects of piracetam and related substances: distinct protective effects against the disturbance of memory following cerebral electroshocks in passive- and active-avoidance tests on mice and rats were noted by *Cumin* et al. (1982) after treatment with aniracetam and piracetam, and by *Mondadori* et al. (1986) after treatment with oxiracetam and piracetam. *Sara* (1980) observed similar responses to etiracetam. *Butler* et al. (1987) described anti-amnestic effects of a whole series of piracetam analogues, including pramiracetam. Numerous observations have also been made of direct positive effects on learning and memory: aniracetam and piracetam (*Yamada* et al., 1985; *Wolthuis*, 1971), etiracetam (*Sara*, 1980) and oxiracetam (*Mondadori* et al., 1986) were found to exert direct effects on acquisition and retention performance in rats and mice in passive- and active-avoidance paradigms; pramiracetam increased the acquisition rate in a 16-armed radial maze (*Murray* and *Fibiger*, 1986) and in a place navigation test (Morris maze) (*Poschel* et al., 1985); positive effects of aniracetam were demonstrated in matching-to-sample tests (*Pontecorvo* et al., 1985). All these findings are supplemented and indirectly supported by observations of a facilitating effect of piracetam on interhemispherical transfer (*Buresova* and *Bures*, 1976), on augmentation of paradoxical sleep in rats (*Wetzel*, 1985), on increased theta power in the hippocampal EEG, and on a reduction in the power of cortical slow waves (*Poschel* et al., 1985).

Interesting and biochemically inexplicable observations indicate that both piracetam and oxiracetam intensify the anticonvulsive effects of anti-epileptics such as carbamazepine (*Mondadori* et al., 1984; *Mondadori* and *Schmutz*, 1986; *Hawkins* and *Mellanby*, 1986).

Biochemical effects of piracetam-like nootropics

There are relatively few data available on the biochemical effects of the piracetam-like nootropics. For a long time, the observation by *Nickolson* and *Wolthuis* (1976) that piracetam stimulates adenylate kinase activity was the sole measured biochemical effect. *Woelk* (1979) then showed that piracetam increased the incorporation of 32P in phosphatidylinositol and phosphatidyl chloride in glia cells and neurons. *Grau* et al. (1987) reported an increase in glucose utilization under hypoxic conditions and accelerated recovery of the EEG. *Poschel* et al. (1983) demonstrated that neither piracetam nor pramiracetam bound to muscarinic cholinergic receptors; nor did binding occur in a dopamine assay with haloperidol. The uptake of GABA and serotonin was not affected by piracetam or by pramiracetam. *Pugsley* et al. (1983) found no evidence of activity in traditional pharmacological assays. No effects were detectable on the concentrations of noradrenaline, dopamine, 5-HT, or 5-HIAA in the cortex or midbrain of the rat. At very high doses (200 mg/kg i.p.), piracetam increased striatal HV without affecting DA levels, indicating that it augments the turnover of DA. Pramiracetam, however, did not increase DA turnover. Receptor assays revealed no affinity of either piracetam or pramiracetam for DA, muscarinic, alpha 1,2- and beta 1,2-adrenergic, 5-HT_1-, 5-HT_2-, GABA, adenosine, and benzodiazepine receptors. On the other hand, it was shown (*Pugsley* et al., 1983; *Shih* and *Pugsley*, 1985) that pramiracetam increased high-affinity choline uptake into hippocampal synaptosomes. The effective doses were 44 and 88 mg/kg i.p.: neither higher nor lower doses were active. Surprisingly enough, piracetam at 100 and 300 mg/kg and aniracetam between 10 and 200 mg/kg both had no effect on high-affinity choline uptake. These results with piracetam are slightly at variance with the observations reported by *Pedata* et al. (1984). These latter authors found that both oxiracetam and piracetam exerted positive effects on high-affinity choline uptake in the rat cortex and hippocampus. The discrepancy may have been due to the timing of the determinations.

The above cholinergic effects are supplemented by findings made by *Spignoli* and *Pepeu* (1986) which demonstrated that oxiracetam prevented the decrease in the acetylcholine content of the cortex and hippocampus induced by cerebral electroshock treatment (piracetam was inactive). Further observations show that piracetam reduces scopolamine-induced amnesia (*Piercey* et al., 1987) and, according to one interesting report (*Pilch* and *Müller*, 1988), elevates the muscarinic cholinergic receptor density in the frontal cortex of aged rats.

Taken as a whole, this selection of findings might at first glance give the impression that the piracetam-like nootropics act by way of cholinergic mechanisms. This conclusion is all the more plausible because there is a very large body of literature on the significance of cholinergic mechanisms in learning and memory (see, for example, *Drachman*, 1978; *Bartus*, 1980). On closer scrutiny of the available results, however, it becomes plainly evident that there is not one single report in which several piracetam-like nootropics tested concurrently have actually been found to produce the same effects. The observed effects, insofar as they have been studied, are not common to all nootropics (*Shih* and *Pugsley*, 1985; *Spignoli* and *Pepeu*, 1986). Considering their similarity in structure as well as in their pharmacological profiles of activity on learning and memory, it seems quite likely (or at least quite possible) that all representatives of this class modulate memory via the same mechanism. Failing any definite evidence to the contrary, this is certainly reason enough to continue the search for one common mechanism of action shared by all the substances belonging to this class.

Are steroids involved in the mediation of nootropic effects?

Even if allowance is made for individual variations dependent on their particular pharmacokinetics, it is still true to say that whenever neuropharmacological agents are administered systemically the brain is flooded with active substance. One may well wonder what chance there is of improving the performance of such a complex and finely tuned organ by so crude a method. On the other hand, there are indications pointing to the existence of endogenous physiological mechanisms that can, under certain circumstances, heigthen the performance of the memory: flash-bulb memories (see e.g. *Brown* and *Kulik*, 1977), i.e. abnormally sharp recollections of certain events mostly associated with highly emotional states, are a good example. If such mechanisms do in fact exist, then they obviously deserve to be regarded as potential targets for pharmacological interventions. In this context, account must also be taken of the possibility that the selective physiological activation of certain neuronal mechanisms in the brain proceeds via peripheral mediators. Nor can one simply dismiss the further possibility that the memory facilitation induced by nootropic drugs may come about through modulation of such processes. Since the pituitary-adrenal axis plays a significant part in emotional states, it seemed important to find out whether piracetam-like nootropics retained their activities in adrenalectomized animals. They did not: oxiracetam, piracetam, aniracetam, and pramiracetam showed no memory-enhancing effects in adrenalectomized mice (*Mondadori* and *Petschke*, 1987). A series of further studies proved that the blockade of their activities was not an effect of dosage: even significantly higher doses of the nootropics were ineffective after adrenalectomy (*Mondadori, Ducret* and *Petschke*, 1989, in press); Accordingly, the next question was whether the products of the adrenal medulla or of the cortex are the critical components in the activity of nootropics. To answer that question the animals were pretreated with aminoglutethimide, which is an inhibitor of several cytochrome-P450-mediated hydroxylation steps in steroid biosynthesis in the adrenal cortex: e.g. 18-hydroxylation of corticosterone (i.e. aldosterone biosynthesis), side-chain cleavage (i.e. conversion of cholesterol to pregnenolone), and 11-hydroxylation (i.e. glucocorticoid biosynthesis) (for a review see *Santen* et al., 1981). Exactly as adrenalectomy, this pretreatment rendered the four piracetam-like nootropics inactive. Aminoglutethimide itself had no effects on the retention performance of the mice. These data provided the first indication of the involvement of products of the adrenal cortex in the mediation of the effects of the piracetam-like nootropics. It must be conceded that aminoglutethimide is not entirely devoid of effects on the adrenal medulla: increases in catecholamine levels have been observed (*Duckworth* and *Kitabchi*, 1971). To exclude this possibility, mice were pretreated with epoxymexrenon. Pretreatment with this specific mineralocorticoid antagonist (*de Gasparo* et al., 1987) gave similar results: the memory-enhancing effects of the piracetam-like nootropics were completely blocked; and again the drug itself had no effect on memory. These findings prove that steroids can play a role in the mediation of nootropic effects. Furthermore, these were the first pharmacological experiments in which all four prototype substances behaved in exactly the same way. (*Mondadori* et al, 1989, in press)

It is interesting to note that certain other substances also lose their memory-modulating activities in the absence of the adrenals: e.g. amphetamine and hydroxyamphetamine (*Martinez* et al., 1980) and vasopressin (*Borell* et al., 1983). However, the effects of these drugs appear to be dependent on the function of the adrenal medulla.

Although autoradiographic studies of the rat brain give the impression that oxiracetam does not readily penetrate the blood-brain barrier (*Mondadori* and *Petschke*, 1987), the above-mentioned findings as a whole cannot be taken as evidence that the piracetam-like nootropics act peripherally. Amongst various other possible mechanisms (see also *Mondadori* and *Petschke*, 1987), it is conceivable that activation of steroid receptors in the brain may be a prerequisite for the efficacy of the piracetam-like nootropics; in other words, steroids may mediate the action of nootropics on memory. The converse is equally plausible, i.e. that these preparations directly or indirectly modulate the effects of certain steroids on memory. There is ample evidence to show that steroids can exert an influence on memory (see for example, *Micheau* et al., 1985; *Bohus* and *de Kloet*, 1981). A new facet emerging from the authors' experiments is that aldosterone-receptor-mediated activity may play a part in memory processing or its regulation.

How these effects come about is unclear; but extrapolation from findings on the peripheral effects of steroids discloses a particularly fascinating aspect. It has been demonstrated that in various organs steroids affect specific gene expression by modulating the rate of transcription of a specific set of genes (*Yamamoto*, 1985; *Schütz*, 1988). It would therefore be extremely interesting to know whether piracetam-like nootropics can exert direct effects on gene transcription, or modulate the action of steroids on gene transcription. There are already a number of publications on the effects of steroids on protein synthesis (*Arenander* and *Vallis*, 1980; *Etgen* et al., 1980; *Nestler* et al., 1981; *Mileusnic* et al., 1986). Since it is known that protein synthesis plays an important part in the formation of memory traces (for a review see *Davies* and

quire, 1984), it is conceivable that nootropics may improve emory via modulation of protein synthesis.

The present observations, which suggest that steroids may be involved in the mediation of the nootropic action of the piracetam derivatives, do not contradict the reported findings on their cholinergic effects, since the possibility that steroids may interact with cholinergic mechanisms cannot simply be dismissed.

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Dr. C. Mondadori

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Picamilon appears to be more effective than Hydergine or vinpocetin in improving blood flow to the cerebral vessels. Picamilon readily crosses the blood-brain barrier to protect neurons against the effects of diminished oxygen flow. It also produces cognitive-enhancing effects.

The combination of these effects provides an entirely new method of dealing safely with several causes of neurological aging. Picamilon is approved as a pharmaceutical product in Russia, but is really a vitamin-like compound consisting of a niacin analog (n-nicotinoyl) uniquely bonded to GABA (gamma aminobutyric acid). When niacin is bound to GABA, it creates a molecule that readily penetrates the blood-brain barrier to enhance cerebral and peripheral circulation. What enables picamilon to work so well is the synergism between the niacin and GABA molecules.

Suggested dose: One tablet, two to three times a day.
If cognitive enhancing results do not occur in 30 days, double the dose.

PIRACETAM

Piracetam is a derivative of the amino acid GABA that increases the sensitivity of receptors in the brain involved in memory and learning. Piracetam is called a nootropic drug because of its ability to enhance the mind. Studies in both animals and humans have demonstrated that Piracetam can improve memory, increase attention and cognition, improve spatial learning, and enhance motor mechanisms. Piracetam is one of the most popular "smart drugs" that is used to increase intelligence, information processing ability, concentration, memory, and creativity. It has been shown to harmonize and synchronize the spheres of the brain by anchoring information within the brain.

Suggested dose: Piracetam should be used in doses ranging from 1600 to 2400 mg a day taken first thing in the morning.

RETIN A

Retin A is a highly publicized vitamin A derivative that stimulates skin cell renewal, increasing the creation of youthful cells at the skin's surface. Retin A may produce side effects such as minor irritation. People using Retin A should stay out of the sun and use a sunblock for normal sunlight exposure, because Retin A increases skin sensitivity to sunlight.

jschoon@clemson.edu

http://www.subnet.co.uk/alpha-aframe.htm

http://www.qhi.co.uk

http://www.eris.com/Nubrain

http://www.2smart.net/nuborne/index.html

TITLE:	Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents.
AUTHOR:	Verbnyi YaI; Derzhiruk LP; Mogilevskii AYa
AUTHOR AFFILIATION:	Physical-Technical Low Temperature Institute, National Academy of Sciences of Ukraine, Khar'kov.
SOURCE:	Neurosci Behav Physiol 1996 Nov-Dec;26(6):507-15
NLM CIT. ID:	97173873
ABSTRACT:	Studies were carried out on the effects of piracetam (4-20 mM) on the electrical activity of identified neurons in the isolated central nervous system of the pond snail in conditions of single-electrode intracellular stimulation and recording. Piracetam-induced changes were seen in 60-70% of the neurons studied. Different parameters showed different sensitivities to piracetam: the most frequent changes were in the action potential generation threshold, the slope and shape of the steady-state voltage-current characteristics of neuron membranes, and the appearance of piracetam-induced transmembrane ion currents. Nifedipine and cadmium ions, both of which are calcium channel blockers, generally reversed or weakened the effects of piracetam on the changes seen in test cells. This indicates that the effects of piracetam result from its action on calcium channels; selective changes in calcium channels may determine which piracetam-induced effects appear at the cellular level. It is hypothesized that the piracetam-sensitive cellular plasticity mechanisms may make a significant contribution to its nootropic action at the behavioral level.
MAIN MESH SUBJECTS:	Lymnaea/*PHYSIOLOGY Neurons/*DRUG EFFECTS Nootropic Agents/ANTAGONISTS & INHIB/*PHARMACOLOGY Piracetam/ANTAGONISTS & INHIB/*PHARMACOLOGY

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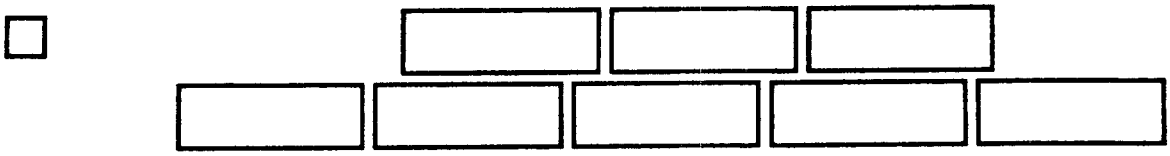
ADDITIONAL MESH SUBJECTS:	**Animal** **Cadmium/PHARMACOLOGY** **Calcium Channel Blockers/PHARMACOLOGY** **Electrophysiology** **Ganglia, Invertebrate/CYTOLOGY/PHYSIOLOGY** **In Vitro** **Membrane Potentials/DRUG EFFECTS/PHYSIOLOGY** **Nifedipine/PHARMACOLOGY** **Parietal Lobe/CYTOLOGY/DRUG EFFECTS** **Patch-Clamp Techniques**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Calcium Channel Blockers)** **0 (Nootropic Agents)** **21829-25-4 (Nifedipine)** **7440-43-9 (Cadmium)** **7491-74-9 (Piracetam)**



National Library of Medicine: IGM Full Record Screen

TITLE: Nootropic drugs and brain cholinergic mechanisms.

AUTHOR: Pepeu G; Spignoli G

AUTHOR AFFILIATION: Department of Preclinical and Clinical Pharmacology, University of Florence, Italy.

SOURCE: Prog Neuropsychopharmacol Biol Psychiatry 1989;13 Suppl:S77-88

NLM CIT. ID: 90139561

ABSTRACT: 1. This review has two aims: first, to marshal and discuss evidences demonstrating an interaction between nootropic drugs and brain cholinergic mechanisms; second, to define the relationship between the effects on cholinergic mechanisms and the cognitive process. 2. Direct or indirect evidences indicating an activation of cholinergic mechanisms exist for pyrrolidinone derivatives including piracetam, oxiracetam, aniracetam, pyroglutamic acid, tenilsetam and pramiracetam and for miscellaneous chemical structures such as vinpocetine, naloxone, ebiratide and phosphatidylserine. All these drugs prevent or revert scopolamine-induced disruption of several learning and memory paradigms in animal and man. 3. Some of the pyrrolidinone derivatives also prevent amnesia associated with inhibition of acetylcholine synthesis brought about by hemicholinium. Oxiracetam prevents the decrease in brain acetylcholine and amnesia caused by electroconvulsive shock. Oxiracetam, aniracetam and pyroglutamic acid prevent brain acetylcholine decrease and amnesia induced by scopolamine. Comparable bell-shaped dose-effect relationships result for both actions. Phosphatidylserine restores acetylcholine synthesis and conditioned responses in aging rats. 4. The mechanisms through which the action on cholinergic systems might take place, including stimulation of the high affinity choline uptake, are discussed. The information available are not yet sufficient to define at which steps of the cognitive process the action on cholinergic system plays a role and which are the influences of the changes in cholinergic function on other neurochemical mechanisms of learning and memory.

MAIN MESH SUBJECTS: Acetylcholine/*METABOLISM
Brain/DRUG EFFECTS/*METABOLISM
Psychotropic Drugs/*PHARMACOLOGY

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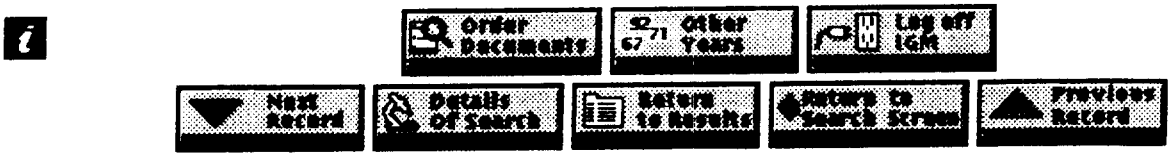
ADDITIONAL MESH SUBJECTS:	**Animal** **Receptors, Cholinergic/DRUG EFFECTS/METABOLISM** **Scopolamine/PHARMACOLOGY** **Synapses/DRUG EFFECTS/PHYSIOLOGY**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, TUTORIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Receptors, Cholinergic)** **51-34-3 (Scopolamine)** **51-84-3 (Acetylcholine)**



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TITLE: Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice.

AUTHOR: Pilch H; Muller WE

AUTHOR AFFILIATION: Psychopharmacological Laboratory, Central Institute of Mental Health, Mannheim, Federal Republic of Germany.

SOURCE: Psychopharmacology (Berl) 1988;94(1):74-8

NLM CIT. ID: 88158509

ABSTRACT: Chronic treatment (2 weeks) with piracetam (500 mg/kg, once daily PO) elevated m-cholinoceptor density in the frontal cortex of aged (18 months) female mice by about 30-40%, but had no effect on m-cholinoceptor density in the frontal cortex of young (4 weeks) mice. The effect of piracetam on m-cholinoceptor density as determined by the specific binding of tritiated QNB was not affected by concomitant daily treatment with either choline (200 mg/kg) or scopolamine (4 mg/kg). It is concluded that the effect of piracetam on m-cholinoceptor density could explain the positive effects which have been reported for combinations of cholinergic precursor treatment with piracetam on memory and other cognitive functions in aged experimental animals and patients and could also represent part of the possible mechanism of action of piracetam alone.

MAIN MESH SUBJECTS:
Aging/*METABOLISM
Cerebral Cortex/DRUG EFFECTS/*METABOLISM
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY
Receptors, Muscarinic/*DRUG EFFECTS

ADDITIONAL MESH SUBJECTS:
Animal
Atropine/PHARMACOLOGY
Female
Male
Mice
Oxotremorine/PHARMACOLOGY
Quinuclidinyl Benzilate/PHARMACOLOGY
Scopolamine/PHARMACOLOGY

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PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Pyrrolidinones)** **0 (Receptors, Muscarinic)** **51-34-3 (Scopolamine)** **51-55-8 (Atropine)** **6581-06-2 (Quinuclidinyl Benzilate)** **70-22-4 (Oxotremorine)** **7491-74-9 (Piracetam)**

http://130.14.32.46/cgi-bin/IGM-client/19819+detail+7

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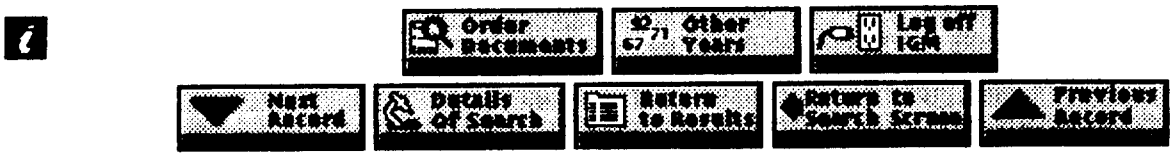
TITLE:	**Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group.**
AUTHOR:	**De Deyn PP; Reuck JD; Deberdt W; Vlietinck R; Orgogozo JM**
AUTHOR AFFILIATION:	**Department of Neurology, Middelheim Hospital, Antwerp, Belgium.**
SOURCE:	**Stroke 1997 Dec;28(12):2347-52**
NLM CIT. ID:	**98074088**

ABSTRACT: BACKGROUND AND PURPOSE: Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients. METHODS: Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n = 927) and in an "early treatment" population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n = 452). RESULTS: In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; P = .15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; P = .07) and Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; P = .02). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score < 55), showed significant improvement on piracetam in both outcomes (P < .02). CONCLUSIONS: Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

MAIN MESH SUBJECTS:
Cerebral Ischemia/*DRUG THERAPY/MORTALITY
Cerebrovascular Disorders/*DRUG THERAPY/MORTALITY
Neuroprotective Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Nootropic Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS:	**Acute Disease** **Aged** **Aged, 80 and over** **Double-Blind Method** **Female** **Human** **Male** **Middle Age** **Support, Non-U.S. Gov't** **Survival Analysis** **Treatment Outcome**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **MULTICENTER STUDY** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Neuroprotective Agents)** **0 (Nootropic Agents)** **7491-74-9 (Piracetam)**



dyslexia

TITLE:	The effects of piracetam in children with dyslexia.
AUTHOR:	Di Ianni M; Wilsher CR; Blank MS; Conners CK; Chase CH; Funkenstein HH; Helfgott E; Holmes JM; Lougee L; Maletta GJ; et al
SOURCE:	J Clin Psychopharmacol 1985 Oct;5(5):272-8
NLM CIT. ID:	86009005
ABSTRACT:	Following previous research which suggests that piracetam improves performance on tasks associated with the left hemisphere, a 12-week, double-blind, placebo-controlled study of developmental dyslexics was conducted. Six study sites treated 257 dyslexic boys between the ages of 8 and 13 years who were significantly below their potential in reading performance. Children were of at least normal intelligence, had normal findings on audiologic, ophthalmologic, neurologic, and physical examination, and were neither educationally deprived nor emotionally disturbed. Piracetam was found to be well tolerated in this study population. Children treated with piracetam showed improvements in reading speed. No other effects on reading were observed. In addition, improvement in auditory sequential short-term memory was observed in those piracetam-treated patients who showed relatively poor memory at baseline. It is suggested that longer term treatment with piracetam may result in additional improvement.
MAIN MESH SUBJECTS:	Dyslexia/*DRUG THERAPY Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE
ADDITIONAL MESH SUBJECTS:	Adolescence Child Clinical Trials Depression/CHEMICALLY INDUCED Human Male Memory Disorders/DRUG THERAPY Memory, Short-Term Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidinones) 7491-74-9 (Piracetam)

TITLE:	Piracetam and dyslexia: effects on reading tests.
AUTHOR:	Wilsher CR; Bennett D; Chase CH; Conners CK; DiIanni M; Feagans L; Hanvik LJ; Helfgott E; Koplewicz H; Overby P; et al
SOURCE:	J Clin Psychopharmacol 1987 Aug;7(4):230-7
NLM CIT. ID:	87308901
ABSTRACT:	Previous research has suggested that dyslexics treated with piracetam have shown improvements in reading skills, verbal memory and verbal conceptualizing ability, feature analysis and processing of letter-like stimuli. Two hundred twenty-five dyslexic children between the ages of 7 years 6 months and 12 years 11 months whose reading skills were significantly below their intellectual capacity were enrolled in a multicenter, 36-week, double-blind, placebo-controlled study. Children of below average intelligence, with abnormal findings on audiologic, ophthalmologic, neurologic, psychiatric, and physical examinations, who were emotionally disturbed or educationally deprived and who had recently been treated with psychoactive medication were excluded from the trial. Piracetam was well tolerated, with no serious adverse clinical or laboratory effects reported. Piracetam-treated children showed significant improvements in reading ability (Gray Oral Reading Test) and reading comprehension (Gilmore Oral Reading Test). Treatment effects were evident after 12 weeks and were sustained for the total period (36 weeks).
MAIN MESH SUBJECTS:	Dyslexia/*DRUG THERAPY/PSYCHOLOGY Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE *Reading
ADDITIONAL MESH SUBJECTS:	Child Clinical Trials Double-Blind Method Female Human Male Random Allocation Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidinones) 7491-74-9 (Piracetam)

Cognitive

TITLE: An overview of pharmacologic treatment of cognitive decline in the aged.

AUTHOR: Reisberg B; Ferris SH; Gershon S

SOURCE: Am J Psychiatry 1981 May;138(5):593-600

NLM CIT. ID: 81204750

ABSTRACT: The most widely known substances that have been investigated for treating cognitive deterioration in the aged are cerebral vasodilators, Gerovital H3, psychostimulants, "nootropics," neuropeptides, and neurotransmitters. The rationale for the choice of specific agents has shifted as our conceptions regarding the origins of cognitive decline have changed; we now know that most cognitive deterioration occurs independently of arteriosclerotic vascular changes. Substances currently being investigated because of their effects on brain electrophysiology, on neurohumoral processes, or on central neurotransmitters show promise.

MAIN MESH SUBJECTS: Cognition Disorders/*DRUG THERAPY

ADDITIONAL MESH SUBJECTS:
Anticoagulants/THERAPEUTIC USE
Clinical Trials
Comparative Study
Dihydroergotoxine/THERAPEUTIC USE
Human
Hyperbaric Oxygenation
Methylphenidate/THERAPEUTIC USE
Parasympathomimetics/THERAPEUTIC USE
Peptides/THERAPEUTIC USE
Piracetam/THERAPEUTIC USE
Procaine/THERAPEUTIC USE
Support, U.S. Gov't, P.H.S. Vasodilator Agents/THERAPEUTIC USE

PUBLICATION TYPES:
CLINICAL TRIAL
JOURNAL ARTICLE
REVIEW

LANGUAGE: Eng

REGISTRY NUMBERS:
0 (Anticoagulants)
0 (Parasympathomimetics)
0 (Peptides)
0 (Vasodilator Agents)
11032-41-0 (Dihydroergotoxine)
113-45-1 (Methylphenidate)
12663-50-2 (Gerovital H3)
59-46-1 (Procaine)
7491-74-9 (Piracetam)

TITLE: Profound effects of combining choline and piracetam on memory enhancement and cholinergic function in aged rats.

AUTHOR: Bartus RT; Dean RL 3d; Sherman KA; Friedman E; Beer B

SOURCE: Neurobiol Aging 1981 Summer;2(2):105-11

NLM CIT. ID: 82058347

ABSTRACT: In an attempt to gain some insight into possible approaches to reducing age-related memory disturbances, aged Fischer 344 rats were administered either vehicle, choline, piracetam or a combination of choline or piracetam. Animals in each group were tested behaviorally for retention of a one trial passive avoidance task, and biochemically to determine changes in choline and acetylcholine levels in hippocampus, cortex and striatum. Previous research has shown that rats of this strain suffer severe age-related deficits on this passive avoidance task and that memory disturbances are at least partially responsible. Those subjects given only choline (100 mg/kg) did not differ on the behavioral task from control animals administered vehicle. Rats given piracetam (100 mg/kg) performed slightly better than control rats (p less than 0.05), but rats given the piracetam/choline combination (100 mg/kg of each) exhibited retention scores several times better than those given piracetam alone. In a second study, it was shown that twice the dose of piracetam (200 mg/kg) or choline (200 mg/kg) alone, still did not enhance retention nearly as well as when piracetam and choline (100 mg/kg of each) were administered together. Further, repeated administration (1 week) of the piracetam/choline combination was superior to acute injections. Regional determinations of choline and acetylcholine revealed interesting differences between treatments and brain area. Although choline administration raised choline content about 50% in striatum and cortex, changes in acetylcholine levels were much more subtle (only 6-10%). No significant changes following choline administration were observed in the hippocampus. However, piracetam alone markedly increased choline content in hippocampus (88%) and tended to decrease acetylcholine levels (19%). No measurable changes in striatum or cortex were observed following piracetam administration. The combination of choline and piracetam did not potentiate the effects seen with either drug alone, and in certain cases the effects were much less pronounced under the drug combination. These data are discussed as they relate to possible effects of choline and piracetam on cholinergic transmission and other neuronal function, and how these effects may reduce specific memory disturbances in aged subjects. The results of these studies demonstrate that the effects of combining choline and piracetam are quite different than those obtained with either drug alone and support the notion that in order to achieve substantial efficacy in aged subjects it may be necessary to reduce multiple, interactive neurochemical dysfunctions in the brain, or affect activity in more than one parameter of a deficient metabolic pathway.

MAIN MESH SUBJECTS:
*Aging
Choline/ANALYSIS/*PHARMACOLOGY
Memory/*DRUG EFFECTS
Parasympathetic Nervous System/*PHYSIOLOGY
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS:	**Acetylcholine/ANALYSIS/SECRETION** **Animal** **Brain Chemistry/DRUG EFFECTS** **Male** **Rats** **Rats, Inbred F344**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Pyrrolidinones)** **51-84-3 (Acetylcholine)** **62-49-7 (Choline)** **7491-74-9 (Piracetam)**

TITLE: Piracetam-induced facilitation of interhemispheric transfer of visual information in rats.

AUTHOR: Buresova O; Bures J

SOURCE: Psychopharmacologia 1976;46(1):93-102

NLM CIT. ID: 76152798

ABSTRACT: The effect of Piracetam (UCB 6215, 2-pyrrolidoneacetamide) on learning mediated by transcommissural information flow was studied in hooded rats. Acquisition of monocular pattern discrimination was faster in drug-treated rats (100 mg/kg, 30 min before training) than in untreated controls. Subsequent relearning with one hemisphere functionally eliminated by cortical spreading depression showed that the strength of the primary engram formed under Piracetam in the hemisphere contralateral to the trained eye remained unaffected but that the secondary trace (in the ipsilateral hemisphere) was considerably improved and almost equalled the primary one (savings increased from 20-30% to 50-60%). Learning with uncrossed optic fibers was unaffected by the drug. Interhemispheric transfer of lateralized visual engrams acquired during functional hemidecortication was facilitated by Piracetam administration preceding the five transfer trials performed with the untrained eye open (imperative transfer). Piracetam was ineffective when the trained eye was open during transfer trials (facultative transfer). After a visual engram had been lateralized by 5 days of monocular overtraining, Piracetam facilitated formation of the secondary engram induced by 3 interocular transfer trials. It is concluded that Piracetam enhances transcommissural encoding mechanisms activated in the initial stage of monocular learning and in some forms of interhemispheric transfer, but does not affect the transcommissural readout. This effect is interpreted as a special case of the Piracetam-induced facilitation of the phylogenetically old mechanisms of redundant information storage which improve liminal or subnormal learning.

MAIN MESH SUBJECTS:	**Form Perception/*DRUG EFFECTS** **Pattern Recognition, Visual/*DRUG EFFECTS** **Piracetam/*PHARMACOLOGY** **Pyrrolidinones/*PHARMACOLOGY** **Transfer (Psychology)/*DRUG EFFECTS**
ADDITIONAL MESH SUBJECTS:	**Animal** **Corpus Callosum/PHYSIOLOGY** **Discrimination Learning/DRUG EFFECTS** **Male** **Memory/DRUG EFFECTS** **Overlearning/DRUG EFFECTS** **Perceptual Masking** **Rats** **Spreading Cortical Depression**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**

☑

TITLE:	Some effects of piracetam (UCB 6215, Nootropyl) on chronic schizophrenia.
AUTHOR:	Dimond SJ; Scammell RE; Pryce IG; Huws D; Gray C
SOURCE:	Psychopharmacology (Berl) 1979 Sep;64(3):341-8
NLM CIT. ID:	80057401
ABSTRACT:	A study is described of effects of a nootropic drug on chronic schizophrenia. The nootropic drugs act on the central nervous system with the cerebral cortex as their target. Chronic schizophrenic patients on the drug showed improvement in object naming and in tests where the patient was required to indicate the number of times he had been tapped. Improvements were also noted in learning and memory tasks. In dichotic listening the patients showed a reduction in the amount of incorrect verbal responses produced. There were no improvements in symptom rating or social behaviour rating. These results suggest some cognitive improvement but little if any change in the disease state of the patient.
MAIN MESH SUBJECTS:	Piracetam/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE Schizophrenia/*DRUG THERAPY
ADDITIONAL MESH SUBJECTS:	Adult Chronic Disease Clinical Trials Dichotic Listening Tests Double-Blind Method Female Human Male Middle Age Motor Skills/DRUG EFFECTS Psychiatric Status Rating Scales Schizophrenic Psychology
PUBLICATION TYPES:	CLINICAL TRIAL JOURNAL ARTICLE
LANGUAGE:	Eng

TITLE:	Increase in the power of human memory in normal man through the use of drugs.
AUTHOR:	Dimond SJ; Brouwers EM
SOURCE:	Psychopharmacology (Berl) 1976 Sep 29;49(3):307-9
NLM CIT. ID:	77079535
ABSTRACT:	Nootropyl (Piracetam) a drug reported to facilitate learning in animals was tested for its effect on man by administering it to normal volunteers. The subjects were given 3x4 capsules at 400 mg per day, in a double blind study. Each subject learned series of words presented as stimuli upon a memory drum. No effects were observed after 7 days but after 14 days verbal learning had significantly increased.
MAIN MESH SUBJECTS:	Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Female Human Male Stimulation, Chemical Verbal Learning/DRUG EFFECTS
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE
LANGUAGE:	Eng

TITLE:	Piracetam facilitates retrieval but does not impair extinction of bar-pressing in rats.
AUTHOR:	Sara SJ; David-Remacle M; Weyers M; Giurgea C
SOURCE:	Psychopharmacology (Berl) 1979 Mar 14;61(1):71-5
NLM CIT. ID:	79180683
ABSTRACT:	Rats were trained on a continuously reinforced bar-press response for water reward. Seven days later they were retested for retention, with or without pretest injection of the nootropic drug, piracetam. Drug-treated animals had significantly shorter response latencies than saline-treated animals. The results are interpreted as a facilitation of retrieval processes after forgetting. The experiment was extended under extinction conditions and it was found that after three sessions there was a tendency to facilitate extinction when response latency is used as the extinction index. The clinical interest of a drug which facilitates the retrieval aspect of the memory process without impairing extinction is discussed.
MAIN MESH SUBJECTS:	Conditioning, Operant/*DRUG EFFECTS Extinction (Psychology)/*DRUG EFFECTS Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Animal Male Rats Water Deprivation
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng

TITLE:	Piracetam impedes hippocampal neuronal loss during withdrawal after chronic alcohol intake.
AUTHOR:	Brandao F; Paula-Barbosa MM; Cadete-Leite A
AUTHOR AFFILIATION:	Department of Anatomy, Porto Medical School, Portugal.
SOURCE:	Alcohol 1995 May-Jun;12(3):279-88
NLM CIT. ID:	95367208
ABSTRACT:	In previous studies we have demonstrated that prolonged ethanol consumption induced hippocampal neuronal loss. In addition, we have shown that withdrawal after chronic alcohol intake augmented such degenerative activity leading to increased neuronal death in all subregions of the hippocampal formation but in the CA3 field. In an attempt to reverse this situation, we tested, during the withdrawal period, the effects of piracetam (2-oxo-1-pyrrolidine acetamide), a cyclic derivative of gamma-aminobutyric acid, as there is previous evidence that it might act as a neuronoprotective agent. The total number of dentate granule, hilar, and CA3 and CA1 pyramidal cells of the hippocampal formation were estimated using unbiased stereological methods. We found out that in animals treated with piracetam the numbers of dentate granule, hilar, and CA1 pyramidal cells were significantly higher than in pure withdrawn animals, and did not differ from those of alcohol-treated rats that did not undergo withdrawal. These data suggest that piracetam treatment impedes, during withdrawal, the pursuing of neuronal degeneration.
MAIN MESH SUBJECTS:	Ethanol/*ADVERSE EFFECTS Hippocampus/*DRUG EFFECTS/PATHOLOGY Neurons/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Substance Withdrawal Syndrome/*PATHOLOGY
ADDITIONAL MESH SUBJECTS:	Analysis of Variance Animal Cell Count/DRUG EFFECTS Diet Male Rats Rats, Sprague-Dawley Support, Non-U.S. Gov't
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	64-17-5 (Ethanol) 7491-74-9 (Piracetam)

TITLE:	Does piracetam counteract the ECT-induced memory dysfunctions in depressed patients?
AUTHOR:	Mindus P; Cronholm B; Levander SE
SOURCE:	Acta Psychiatr Scand 1975 Jun;51(5):319-26
NLM CIT. ID:	75201625
ABSTRACT:	A double-blind, intra-individual cross-over comparison of the effect of piracetam on retrograde memory impairement as measured by the KS memory test battery was performed in connection with second and third Bi-ECT in 18 patients diagnosed as suffering from depression. The seizure duration and the post-ECT EGG patterns were examined visually and the post-ECT confusion time was measured. Piracetam was given orally in the dose of 4.8 g/day for 3 days. No significant effects were obtained on memory scores, electrical stimulus duration, EEG pattern or post-ECT confusion time. The findings may indicate that the protective effect of piracetam shown in animal electroconvuslive stimulation (ECS) is due to a counteraction of the disturbing effect of hypoxia on memory functions. It is concluded that more information is needed as regards the pharmacokinetics and the mode of action of the drug.
MAIN MESH SUBJECTS:	Depression/*THERAPY Electroconvulsive Therapy/*ADVERSE EFFECTS Memory/*DRUG EFFECTS Memory Disorders/*ETIOLOGY/PREVENTION & CONTROL Piracetam/*PHARMACOLOGY/THERAPEUTIC USE Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Adult Aged Clinical Trials Drug Evaluation English Abstract Female Human Male Middle Age Placebos
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE
LANGUAGE:	Eng

TITLE:	Effects of oxiracetam on learning and memory in animals: comparison with piracetam.
AUTHOR:	Mondadori C; Classen W; Borkowski J; Ducret T; Buerki H; Schade A
SOURCE:	Clin Neuropharmacol 1986;9 Suppl 3:S27-38
NLM CIT. ID:	87244092
ABSTRACT:	The effects of oxiracetam and piracetam were compared in learning and memory tests in rats and mice. In the dose range examined, the two nootropics were equally active in reducing the amnesia induced by cerebral electroshock in the mouse. Step-down retention performance, however, was distinctly improved by oxiracetam but unaffected by piracetam, no matter whether it was given before or immediately after the learning trial. Oxiracetam also improved acquisition performance in aged (24- to 27-month-old) rats in an active-avoidance situation at doses of 30 and 100 mg/kg i.p. whereas piracetam showed no effect at 100 mg/kg i.p.
MAIN MESH SUBJECTS:	Avoidance Learning/*DRUG EFFECTS Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidines/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Aging/PHYSIOLOGY Animal Comparative Study Drug Administration Schedule Electroshock Mice Rats
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidines) 0 (Pyrrolidinones) 62613-82-5 (oxiracetam) 7491-74-9 (Piracetam)

A. INGREDIENT NAME:

QUINACRINE HYDROCHLORIDE

B. Chemical Name:

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride; Mepacrine Hydrochloride; Quinacrinium Chloride
2-Chloro-5-(Omega-Diethylamino-Alpha-Methylbutylamino)-7-Methoxyacridine Dihydrochloride
3-Chloro-9-(4'-Diethylamino-1'-Methylbutylamino)-7-Methoxyacridine Dihydrochloride
6-Chloro-9-((4-(Diethylamino)-1-Methylbutyl)Amino)-2-Methoxyacridine Dihydrochloride
3-Chloro-7-Methoxy-9-(1-Methyl-4-Diethylaminobutylamino)Acridine Dihydrochloride
2-Methoxy-6-Chloro-9-(4-Diethylamino-1-Methylbutylamino)

C. Common Name:

Acrichine, Acriquine, Akrichin (Czech), Arichin, Atabrine, Atabrine Dihydrochloride, Atabrine Hydrochloride, Atebrin, Atebrine, AtebrinHydrochloride, Chemiochin, Chinacrin, Chinacrin Hydrochloride, Crinodora, Dial, Erion, Italchin, malaricida, Mecryl, Mepacrine Dihydrochloride, Mepacrine Hydrochloride, Methoquine, Acridine Dihydrochloride, Metochin, Metoquin, Metoquine, Palacrin, Palusan, Pentilen, Quinacrine Dihydrochloride, Quinacrine Hydrochloride

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 100.12%
98 %

E. Information about how the ingredient is supplied:

Bright Yellow, Crystalline Powder. It is odorless and has a bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

Pharmacopeias. In Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., It., Mex., Neth., Nord., Pol., Rus., Span., Swiss., Turk., and U. S.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Tablets

I. Information about strength:

100mg - 900mg

J. Information about route of administration:

Orally

K. Stability data:

Melting Point: 257 C (DEC)
Incompatible with alkalis, nitrates, and oxidizing agents.

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

The Drugs & Cosmetics Act 1940 and the rules thereunder

From 39 Rule 150 E (f)

Certificate No. VCL/ 17/97-98.

30-2193
53219

1. Name of the manufacturer : M/s. Vipor Chemicals, Baroda-390 010.
2. Licence No. : G/152
3. Date of Receipt : 03-07-97.
4. Name of Sample : HEPACRINE HYDROCHLORIDE B.P.
5.

(a) Batch No.	(b) Quantity Submitted	(c) Total Quantity Mfgd/Purchased	(d) Date of Manufacture	(e) Date of Expiry
025	2x 15gm.	-	JULY'97	JUNE'2002

6. RESULTS OF ANALYSIS — As per B.P.

Description	: Yellow Crystalline Powder
Solubility	: Comply
Identification	: A, B, C, D Comply
Acidity	: PH of 2% Solution : 4.0
3-Chloro -7-Methoxy Acridine	: Complies
Water	: 006.8 %
Sulphated Ash	: 000.07%
Assay	: 100.1%

D

9/97

Report : In the opinion of the undersigned, the sample referred to above is of STANDARD QUALITY/ is ~~NOT OF STANDARD QUALITY~~ as defined in the Act and the rules made thereunder.

The opinion is in respect of the tests carried out and mentioned above.

QUALITY CONTROL REPORT

CHEMICAL NAME.: QUINACRINE HYDROCHLORIDE USP

MANUFACTURE LOT NO.: 025

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
BRIGHT YELLOW, CRYSTALLINE POWDER. IS ODORLESS AND HAS A BITTER TASTE.

2) SOLUBILITY.:
SPARINGLY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL.

3) MELTING POINT.:
MELTS AT ABOUT 250 DEGREES WITH DECOMPOSITION.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES (A) AS PER IR SPECTRUM USP XXII.
B) COMPLIES (C) AS PER USP XXII.
C) A SOLUTION 1 IN 100 HAS A PH ABOUT 4.5.

PASSES.: _____ **FAILS.:** _____

COMMENTS.: QUINACRINE DIHYDROCHLORIDE IS ALSO KNOWN AS QUINACRINE HCL.

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: 22299-2 NAME: QUINACRINE DIHYDROCHLORIDE HYDRATE, 98%

CAS #: 69-05-6

MF: C23H30CLN3O

SYNONYMS

ACRICHINE * ACRIQUINE * AKRICHIN (CZECH) * ARICHIN * ATABRINE * ATABRINE DIHYDROCHLORIDE * ATABRINE HYDROCHLORIDE * ATEBRIN * ATEBRINE * ATEBRIN HYDROCHLORIDE * CHEMIOCHIN * CHINACRIN * CHINACRIN HYDROCHLORIDE *

(2-CHLORO-5-(OMEGA-DIETHYLAMINO-ALPHA-METHYLBUTYLAMINO) -7-METHOXYACRIDINE DIHYDROCHLORIDE *

3-CHLORO-9-(4'-DIETHYLAMINO-1'-METHYLBUTYLAMINO)-7-METHOXYACRIDINE DIHYDROCHLORIDE *

6-CHLORO-9-((4-(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-METHOXYACRIDINE DIHYDROCHLORIDE *

3-CHLORO-7-METHOXY-9-(1-METHYL-4-DIETHYLAMINOBUTYLAMINO)ACRIDINE DIHYDROCHLORIDE *

CRINODORA * DIAL * ERION * ITALCHIN * MALARICIDA * MECRYL * MEPACRINE DIHYDROCHLORIDE * MEPACRINE HYDROCHLORIDE * METHOQUINE *

(2-METHOXY-6-CHLORO-9-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO) ACRIDINE DIHYDROCHLORIDE * METOCHIN * METOQUIN * METOQUINE * PALACRIN * PALUSAN * PENTILEN * QUINACRINE DIHYDROCHLORIDE * QUINACRINE HYDROCHLORIDE * 866 R.P. * SN 390 *

---------- TOXICITY HAZARDS ----------

RTECS NO: AR7875000

ACRIDINE, 6-CHLORO-9-((4-(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-METHOXY-, DIHYDROCHLORIDE

TOXICITY DATA

ORL-RAT LD50:660 MG/KG	JPETAB 91,157,47
IVN-RAT LD50:29 MG/KG	JPETAB 91,157,47
IUT-RAT LD50:100 MG/KG	IJEBA6 16,1074,78
ORL-MUS LD50:557 MG/KG	JPETAB 91,157,47
IPR-MUS LD50:189 MG/KG	JPETAB 91,133,47
SCU-MUS LD50:212 MG/KG	ABEMAV 1,317,41

IVN-MUS LD50:38 MG/KG JPETAB 91,157,47
ORL-RBT LD50:433 MG/KG JPETAB 91,157,47
IVN-RBT LD50:9 MG/KG JPETAB 91,157,47
IVN-GPG LD50:14 MG/KG JPETAB 91,157,47

REVIEWS, STANDARDS, AND REGULATIONS
NOES 1983: HZD X4102; NIS 1; TNF 66; NOS 3; TNE 987; TFE 508
EPA GENETOX PROGRAM 1988, NEGATIVE: SPERM MORPHOLOGY-MOUSE

EPA GENETOX PROGRAM 1988, INCONCLUSIVE: MAMMALIAN MICRONUCLEUS

TARGET ORGAN DATA
PERIPHERAL NERVE AND SENSATION (FLACCID PARALYSIS WITHOUT ANESTHESIA)
BEHAVIORAL (ALTERED SLEEP TIME)
BEHAVIORAL (SOMNOLENCE)
BEHAVIORAL (TOXIC PSYCHOSIS)
BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)
VASCULAR (OTHER CHANGES)
LUNGS, THORAX OR RESPIRATION (RESPIRATORY DEPRESSION)
LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)
IMMUNOLOGICAL INCLUDING ALLERGIC (ANAPHYLAXIS)
PATERNAL EFFECTS (SPERMATOGENESIS)
MATERNAL EFFECTS (OVARIES, FALLOPIAN TUBES)
MATERNAL EFFECTS (UTERUS, CERVIX, VAGINA)
MATERNAL EFFECTS (MENSTRUAL CYLCE CHANGES OR DISORDERS)
MATERNAL EFFECTS (OTHER EFFECTS ON FEMALE)
EFFECTS ON FERTILITY (FEMALE FERTILITY INDEX)
EFFECTS ON FERTILITY (PRE-IMPLANTATION MORTALITY)
EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)
DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS
HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
MAY CAUSE EYE IRRITATION.
MAY CAUSE SKIN IRRITATION.
TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID
IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS OF
WATER FOR AT LEAST 15 MINUTES.

IN CASE OF CONTACT, IMMEDIATELY WASH SKIN WITH SOAP AND COPIOUS

AMOUNTS OF WATER.
IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
WASH CONTAMINATED CLOTHING BEFORE REUSE.

---------- PHYSICAL DATA ----------

MELTING PT: 257 C (DEC)

APPEARANCE AND ODOR
YELLOW POWDER

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA
WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

INCOMPATIBILITIES
STRONG OXIDIZING AGENTS
STRONG ACIDS
MAY DISCOLOR ON EXPOSURE TO LIGHT.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
NITROGEN OXIDES
HYDROGEN CHLORIDE GAS

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
EVACUATE AREA.
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN

IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

CHEMICAL SAFETY GOGGLES.
RUBBER GLOVES.
NIOSH/MSHA-APPROVED RESPIRATOR.
SAFETY SHOWER AND EYE BATH.
USE ONLY IN A CHEMICAL FUME HOOD.
DO NOT BREATHE DUST.
DO NOT GET IN EYES, ON SKIN, ON CLOTHING.
WASH THOROUGHLY AFTER HANDLING.
TOXIC.
KEEP TIGHTLY CLOSED.
LIGHT SENSITIVE
STORE IN A COOL DRY PLACE.
HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

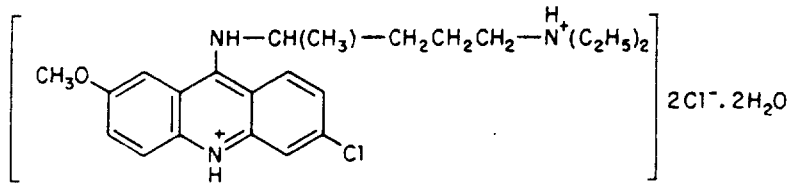
WEAR SUITABLE PROTECTIVE CLOTHING.

Packaging and storage—Preserve Pyroxylin loosely packed in cartons, protected from light.

CATEGORY—Pharmaceutic necessity for COLLODION.

QUINACRINE HYDROCHLORIDE

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride; Mepacrine Hydrochloride; Quinacrinium Chloride



$C_{23}H_{30}ClN_3O.2HCl.2H_2O$ Mol. wt. 508.94

Quinacrine Hydrochloride contains not less than 98 per cent of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Description—Quinacrine Hydrochloride occurs as a bright yellow, crystalline powder. It is odorless and has a bitter taste.

Solubility—One Gm. of Quinacrine Hydrochloride dissolves in about 35 ml. of water. It is soluble in alcohol.

Identification—

A: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add a slight excess of ammonia T.S.: a yellow to orange, oily precipitate of quinacrine base is formed which adheres to the wall of the vessel and is soluble in ether.

B: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of diluted nitric acid: a yellow crystalline precipitate is formed.

C: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of mercuric chloride T.S.: a yellow precipitate is formed.

D: The filtrate from the precipitate, obtained in *Identification test A*, acidified with nitric acid, responds to the tests for *Chloride*, page 901.

pH—The pH of a solution of Quinacrine Hydrochloride (1 in 100) is about 4.5.

Water, page 942—Determine the water content of Quinacrine Hydrochloride by drying at 105° for 4 hours or by the Karl Fischer method: it contains not less than 6 per cent and not more than 8 per cent of water.

Residue on ignition, page 912—The residue on ignition of 200 mg. of Quinacrine Hydrochloride is negligible.

Assay—Transfer to a 100-ml. volumetric flask about 250 mg. of Quinacrine Hydrochloride, accurately weighed, dissolve it in 10 ml. of water, then add 10 ml. of a solution prepared by dissolving 25 Gm. of sodium acetate and 10 ml. of glacial acetic acid in water to make 100 ml. Add exactly 50 ml. of 0.1 *N* potassium dichromate and water to make 100 ml., stopper the flask, mix thoroughly, and filter through a dry filter paper into a dry flask, rejecting the first 15 ml. of the filtrate. Measure 50 ml. of the subsequent filtrate into a glass-stoppered flask, add 15 ml. of hydrochloric acid and 20 ml. of potassium iodide T.S., stopper the flask, mix the contents gently, and allow to stand in the dark for 5 minutes. Add 75 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is neared. Perform a blank determination with the same quanti-

ties of the same reagents and in the same manner (see *Residual Titrations*, page 832). Each ml. of 0.1 *N* potassium dichromate is equivalent to 8.482 mg. of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Packaging and storage—Preserve Quinacrine Hydrochloride in tight, light-resistant containers.

CATEGORY—Anthelmintic; antimalarial; antiprotozoan.

DOSE—USUAL—Suppressive—

Antimalarial—100 mg.

Therapeutic—

Antimalarial and antiprotozoan—200 mg. every 6 hours for 5 doses, then 100 mg. three times a day for 6 days.

Anthelmintic—500 mg. with 500 mg. of sodium bicarbonate in a single dose.

Quinacrine Hydrochloride Tablets

QUINACRINE HYDROCHLORIDE TABLETS

Quinacrine Hydrochloride Tablets contain not less than 93 per cent and not more than 107 per cent of the labeled amount of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Identification—

A: Powder a sufficient number of Quinacrine Hydrochloride Tablets, equivalent to about 250 mg. of quinacrine hydrochloride, and extract with two 15-ml. portions of hot water, filtering after each extraction. To 5 ml. of the extract add ammonia T.S., and remove the oily precipitate so formed by extraction with two 10-ml. portions of ether. The water layer, acidified with nitric acid, responds to the tests for *Chloride*, page 901.

B: To the remaining portion of the water extract obtained in *Identification test A* add 2 ml. of ammonia T.S.: a yellow, oily precipitate forms. Shake the mixture with several 10-ml. portions of chloroform until the water layer is practically colorless. Evaporate the combined chloroform solutions on a steam bath in a small beaker, and add to the residue 3 ml. of hot water and 2 ml. of diluted hydrochloric acid, moistening the sides of the beaker with the liquid and stirring with a glass rod. Allow to stand for 30 minutes, then filter, wash the crystals with ice-cold water until the last washing is practically neutral to litmus, and dry at 105° for 2 hours: the crystals so obtained respond to *Identification tests B* and *C* under *Quinacrine Hydrochloride*, page 599.

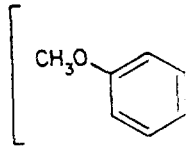
Disintegration—Quinacrine Hydrochloride Tablets meet the requirements of the *Disintegration Test for Tablets*, page 936, in not more than 1 hour.

Weight variation—Quinacrine Hydrochloride Tablets meet the requirements of the *Weight Variation Test for Tablets*, page 945.

Assay—Weigh a counted number of not less than 20 Quinacrine Hydrochloride Tablets, and reduce them to a fine powder without appreciable loss. Weigh accurately a portion of the powder, equivalent to about 200 mg. of quinacrine hydrochloride, and place it in a separator with 25 ml. of water and 3 ml. of diluted hydrochloric acid. Extract the suspension with two 15-ml. portions of chloroform, and wash the chloroform extracts in a second separator with 10 ml. of water. Discard the washed chloroform, and add the water in the second separator to the suspension of tablet

material. Make the
pletely with successiv
extract is colorless.
cotton moistened with
form. Gently evapor
15 minutes. To the re
steam bath until the
pletely with the aid of
proceed as directed in
ning with "then add 10
is equivalent to 8.482
Packaging and storage—
tainers.
Tablets available—Quin
following amounts of q

CATEGORY and Do



$(C_{20}H_{24}N_2O_2)_2.H_2SO_4$

Quinidine Sulfate
species of *Cinchona*
Flückiger (Fam. *Rub*

Description—Quinidine
cohering in masses. It
to light. Its solutions
Solubility—One Gm. of
about 10 ml. of alcoho
Identification—
A: Acidify a solution
ing solution has
B: To 5 ml. of a solu
mine T.S., and
green color due
C: To 5 ml. of a solu
T.S., and stir w
interval (distin
D: Quinidine Sulfate
Specific rotation, page 8
the anhydrous basis,
Quinidine Sulfate in e

1378-w

...quine. Cyclochin; Haloquine. 4-(7-Chloro-4-...lamino)-2,6-bis(dihexylaminomethyl)phenol. ...ClN$_4$O=497.1.

CAS — 14594-33-3.

A yellow crystalline powder with a bitter taste. Practically **insoluble** in water; readily soluble in dilute acids; insoluble in dilute alkalis. **Protect** from light.

Uses. Cycloquine resembles chloroquine in its action and has been used in the USSR for the suppression and treatment of malaria. A dose of 300 mg has been given weekly for the suppression of malaria and 300 mg has been given daily for three days in the treatment of acute attacks.

1379-e

Diformyldapsone. DFD; DFDDS; Diformyldiaminodiphenylsulphone. 4,4'-Sulphonylbisformanilide. $C_{14}H_{12}N_2O_4S$=304.3.

CAS — 6784-25-4.

A crystalline solid. M.p. 267° to 269°. Practically **insoluble** in water; soluble 1 in about 200 of dimethyl sulphoxide. It is most stable at pH 6.

Uses. Diformyldapsone has been used as an antimalarial in doses of 400 to 800 mg weekly, but is given with chloroquine, primaquine, or pyrimethamine, since it has no action on gametocytes.

Diformyldapsone had an approximate half-life of 84 hours.— W. Peters, *Postgrad. med. J.*, 1973, *49*, 573.

Diformyldapsone in doses of 3.2 g twice weekly for 4 weeks damaged the red blood cells in 25 subjects. Smaller doses did not appear to cause haemolysis.— S. A. Cucinell *et al.*, *J. clin. Pharmac.*, 1974, *14*, 51.

Malaria. Diformyldapsone was considered to protect volunteers more effectively against the Vietnam Smith st... of *P. falciparum* than against the Chesson strain ... *vivax*. There were no reports of met...binaemia in patients receiving diformyldapsone ... in conjunction with chloroquine.— Clyde. D.F. *et al.*, *Milit. Med.*, 1971, *136*, 836, per *Trop. Dis. Bull.*, 1972, *69*, 593. See also *idem*, *Milit. Med.*, 1970, *135*, 527.

Diformyldapsone 100 to 800 mg weekly given with chloroquine alone, or with chloroquine and primaquine, suppressed the Smith strain of falciparum malaria in 41 of 45 men and the Brai. strain in 9 men. The combination appeared to be more effective than treatment with chloroquine and primaquine, or than pyrimethamine 25 mg weekly which suppressed the Brai. but not the Smith strain.— D. F. Clyde *et al.*, *Am. J. trop. Med. Hyg.*, 1971, *20*, 1, per *Trop. Dis. Bull.*, 1971, *68*, 1153.

Diformyldapsone given weekly with chloroquine protected 5 of 8 volunteers against falciparum malaria. Better results were noted when volunteers were given dapsone daily with chloroquine or chloroquine and primaquine weekly.— D. Willerson, *Am. J. trop. Med. Hyg.*, 1972, *21*, 138, per *J. Am. med. Ass.*, 1972, *220*, 1382.

Diformyldapsone, 400 to 800 mg with pyrimethamine 25 mg, both given weekly, was considered to provide effective prophylaxis against chloroquine-resistant *P. falciparum* and against *P. vivax*. No toxic side-effects were noted.— D. F. Clyde *et al.*, *Milit. Med.*, 1973, *138*, 418, per *Trop. Dis. Bull.*, 1974, *71*, 15.

1380-b

Hydroxychloroquine Sulphate *(B.P.)*

Hydroxychloroquine Sulfate *(U.S.P.)*; Oxichlorochin Sulphate; Win 1258-2. 2-{N-[4-(7-Chloro-4-quinolylamino)pentyl]-N-ethylamino}ethanol sulphate.

$C_{18}H_{26}ClN_3O, H_2SO_4$=433.9.

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (...te).

Ph...poeias. In *Br.* and *U.S.*

A ...e or almost white odourless crystalline powder with a bitter taste. There are 2 forms, one melting at about 198° and the other at about 240°. Hydroxychloroquine sulphate 100 mg is approximately equivalent to 77 mg of hydroxychloroquine base. **Soluble** 1 in 5 of water; practically insoluble in alcohol, chloroform, and ether. A 1% solution in water has a pH of 3.5 to 5.5. **Protect** from light.

Adverse Effects, Treatment, Precautions, and Resistance. As for Chloroquine, p.395.

Hydroxychloroquine was given in an average dose of 800 mg daily for up to 4½ years to 94 patients with lupus erythematosus, rheumatoid arthritis, or scleroderma. The patients had not previously received chloroquine, amodiaquine, mepacrine, or quinine. Corneal deposition occurred in 26 patients; it was reversible in 20, persistent in 3, and 3 were lost to follow-up. There was a rapid rise in incidence after 150 g had been given. One patient who had received 770 g over 26½ months developed retinopathy. A second case of probable retinopathy was subsequently seen in a further patient.— R. V. Shearer and E. L. Dubois, *Am. J. Ophthal.*, 1967, *64*, 245.

Ocular toxicity in 3 of 99 patients after long-term treatment with hydroxychloroquine.— R. I. Rynes *et al.*, *Arthritis Rheum.*, 1979, *22*, 832.

Uses. Hydroxychloroquine sulphate has an antimalarial action similar to that of chloroquine (see p.396) but it is mainly used in the treatment of systemic and discoid lupus erythematosus and rheumatoid arthritis. Treatment is usually started with about 400 to 800 mg daily in divided doses with meals and the dose is reduced to about 200 to 400 mg when a response occurs. In malaria, a suppressive dose of 400 mg every 7 days is used, and in treating an acute attack a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days. Children may be given a weekly suppressive dose equivalent to 5 mg of base per kg body-weight, while for treatment an initial dose of 10 mg per kg may be given, following by 5 mg per kg 6 hours later and again on the second and third days.

In the treatment of giardiasis, the usual dose is 200 mg thrice daily for 5 days.

Hydroxychloroquine sulphate has been used in the treatment of polymorphous light eruptions. The dose is as for rheumatoid arthritis.

Porphyria. Hydroxychloroquine, 400 mg weekly for several months, had been reported to be safe and effective in the treatment of porphyria cutanea tarda.— F. De Matteis, *Br. J. Derm.*, 1972, *87*, 174.

Thrombo-embolic disorders. Of 565 patients who underwent surgery 284 received an injection of hydroxychloroquine sulphate 200 mg with their premedication and then 200 mg eight-hourly by mouth or by injection until discharge from hospital. From postoperative observations and by phlebography it appeared that hydroxychloroquine could be useful in reducing the incidence of deep-vein thrombosis and pulmonary embolism.— A. E. Carter *et al.*, *Br. med. J.*, 1971, *1*, 312.

The incidence of deep-vein thrombosis after surgery was 5% in 107 patients given hydroxychloroquine sulphate compared with 16% in 97 controls. The dose was 1.2 g by mouth in 3 divided doses in the 24 hours before surgery followed by 400 mg every 12 hours after surgery until discharge.— A. E. Carter and R. Eban, *Br. med. J.*, 1974, *3*, 94.

For discussions, see A. S. Gallus and J. Hirsh, *Drugs*, 1976, *12*, 132; A. G. G. Turpie and J. Hirsh, *Br. med. Bull.*, 1978, *34*, 183.

Preparations

Hydroxychloroquine Sulfate Tablets *(U.S.P.)*. Tablets containing hydroxychloroquine sulphate.

Hydroxychloroquine Tablets *(B.P.)*. Tablets containing hydroxychloroquine sulphate. They are sugar-coated.

Plaquenil *(Winthrop, UK)*. Hydroxychloroquine sulphate, available as tablets of 200 mg. (Also available as Plaquenil in *Austl., Austral., Belg., Canad., Denm., Fin., Fr., Iceland, Ital., Neth., Norw., Swed., Switz., USA*).

Other Proprietary Names

Ercoquin *(Denm., Norw., Swed.)*; Quensyl *(Ger.)*.

1381-v

Mefloquine Hydrochloride. WR 142490.

(±)-α-[2,8-Bis(trifluoromethyl)-4-quinolyl]-α-(2-piperidyl)methanol hydrochloride.

$C_{17}H_{16}F_6N_2O, HCl$=414.8.

CAS — 53230-10-7 (mefloquine); 51773-92-3 (hydrochloride).

Adverse Effects. Epigastric discomfort has been reported after doses of 1 g, and nausea and dizziness after doses of 1.75 or 2 g.

Uses. Mefloquine hydrochloride is a 4-quinolinemethanol compound which has schizonticidal activity against malaria parasites. It is active against chloroquine-resistant falciparum malaria.

Malaria. A preliminary study in 17 subjects of the use of mefloquine hydrochloride in single 1-g doses as a prophylactic against drug-resistant malaria.— K. H. Rieckmann *et al.*, *Bull. Wld Hlth Org.*, 1974, *51*, 375.

Thirty-five non-immune volunteers infected with 1 of 3 strains of *Plasmodium falciparum*, 2 of them drug-resistant, were treated with a single oral dose of mefloquine hydrochloride 0.4, 1, or 1.5 g. The infection was cured in 2 of 12 given 0.4 g, 13 of 15 given 1 g, and 8 of 8 given 1.5 g. In 5 partially-immune volunteers infected with *P. vivax* cures were achieved with single doses of 0.4 or 1 g in two, but infection reappeared in the remaining 3 subjects and was subsequently cured with chloroquine and primaquine.— G. M. Trenholme *et al.*, *Science*, 1975, *190*, 792.

None of 21 volunteers bitten by 10 to 15 mosquitoes heavily infected with *P. falciparum* developed malaria when given mefloquine hydrochloride 250 or 500 mg weekly, 500 mg every 2 weeks, or 1 g every 4 weeks. Doses of 250 mg weekly suppressed *P. vivax* infections during drug administration but malaria appeared when treatment ceased.— D. F. Clyde *et al.*, *Antimicrob. Ag. Chemother.*, 1976, *9*, 384.

Of 39 patients with chloroquine-resistant falciparum malaria, 36 (92%) were cleared of infection with no recrudescence after treatment with quinine, sulfadoxine, and pyrimethamine, by the regimen of A.P. Hall (*Br. med. J.*, 1975, *2*, 15; see under Quinine, p.405), while all of 35 were cleared by treatment with quinine followed by a single dose of mefloquine hydrochloride 1.5 g (one patient received only 1 g). Side-effects in 40 patients given mefloquine were: abdominal pain (7), anorexia (6), diarrhoea (6), dizziness (9), nausea (3), vomiting (9), and weakness (3). Side-effects were minimal or absent if at least 12 hours elapsed after the last dose of quinine.— A. P. Hall *et al.*, *Br. med. J.*, 1977, *1*, 1626.

Animal studies of the antimalarial activities of 4-quinolinemethanols including mefloquine and a report of the US Army Malaria Research Program.— L. H. Schmidt *et al.*, *Antimicrob. Ag. Chemother.*, 1978, *13*, 1011.

Of 37 patients with chloroquine-resistant falciparum malaria all were radically cured by a single dose of mefloquine hydrochloride 1.5 g. Side-effects (nausea, vomiting, diarrhoea, dizziness, headache) could probably be reduced by a formulation designed to slow absorption.— E. B. Doberstyn *et al.*, *Bull. Wld Hlth Org.*, 1979, *57*, 275.

Metabolism. Preliminary study in 1 subject given a single dose of mefloquine indicated relatively rapid absorption, extensive distribution, and prolonged elimination phases. Mefloquine was reported to be extensively bound to plasma proteins and to be concentrated in erythrocytes.— J. M. Grindel *et al.*, *J. pharm. Sci.*, 1977, *66*, 834.

The kinetics of mefloquine hydrochloride.— R. E. Desjardins *et al.*, *Clin. Pharmac. Ther.*, 1979, *26*, 372.

1382-g

Mepacrine Hydrochloride *(B.P., Eur. P.)*

Mepacrini Hydrochloridum; Acrinamine; Quinacrine Hydrochloride *(U.S.P.)*; Quinacrinium Chloride; Acrichinum; Antimalarinae Chlorhydras; Chinacrina. 6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.

$C_{23}H_{30}ClN_3O, 2HCl, 2H_2O$=508.9.

CAS — 83-89-6 (mepacrine); 69-05-6 (dihydrochloride, anhydrous); 6151-30-0 (dihydrochloride, dihydrate).

Pharmacopoeias. In *Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., Int., It., Mex., Neth., Nord., Pol., Rus., Span., Swiss, Turk.*, and *U.S.*

A bright yellow odourless crystalline powder with a bitter taste. M.p. about 250° with decomposition. **Soluble** 1 in 35 to 40 of water; soluble in alcohol; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in acetone and ether. A 2% solution in water has a pH of 3 to 5. **Incompatible** with alkalis, nitrates, and oxidising agents. **Store** in airtight containers. Protect from light.

Incompatibility. Mepacrine hydrochloride was incompatible with amaranth, benzylpenicillin, sodium alginate, sodium aminosalicylate, sodium carboxymethylcellulose, sodium lauryl sulphate, and thiomersal.— *J. Am. pharm. Ass., pract. Pharm. Edn*, 1952, *13*, 658.

Adverse Effects. Minor effects liable to arise with ordinary doses are dizziness, headache, and mild gastro-intestinal disturbances. Most patients develop a yellow discoloration of the skin. Large doses may give rise to nausea and vomiting and occasionally to transient mental disturbances. A few patients develop chronic dermatoses after prolonged administration of the drug; these may be either lichenoid, eczematoid, or exfoliative in type. Deaths from exfoliative dermatitis and from hepatitis have been reported. The use of mepacrine over prolonged periods may give rise to aplastic anaemia.

Adverse effects of intrapleural instillation include fever and chest pain caused by the inflammatory reaction.

The toxicity arising from prolonged administration has contributed to the decline in the use of mepacrine in malaria.

Two patients had convulsions a few hours after the intrapleural administration of mepacrine hydrochloride 400 mg for malignant effusions. One developed status epilepticus and died; the other was successfully controlled with phenobarbitone intravenously and phenytoin by mouth.— I. Borda and M. Krant, *J. Am. med. Ass.*, 1967, *201*, 1049.

Mepacrine hydrochloride 100 mg daily had been reported to cause haemolytic anaemia in certain individuals with a deficiency of glucose-6-phosphate dehydrogenase. The reaction was not considered clinically significant under normal circumstances (e.g. in the absence of infection).— E. Beutler, *Pharmac. Rev.*, 1969, *21*, 73.

A patient with rheumatoid arthritis treated with mepacrine hydrochloride for about 20 years had developed a blue-black discoloration of the hard palate, the nail beds, and the skin over the shins. The colour disappeared when mepacrine was stopped and reappeared when it was restarted.— M. J. Egorin *et al.*, *J. Am. med. Ass.*, 1976, *236*, 385.

Treatment of Adverse Effects. As for Chloroquine, p.396.

Precautions. Mepacrine enhances the toxicity of the 8-aminoquinoline derivatives such as primaquine by inhibiting their metabolism.

Mepacrine might interfere with fluorimetric estimations of plasma hydrocortisone.— J. Millhouse, *Adverse Drug React. Bull.*, 1974, Dec., 164.

Absorption and Fate. Mepacrine is absorbed from the gastro-intestinal tract and appears in the blood within 2 hours. It becomes concentrated in liver, pancreas, spleen, and lung, and higher concentrations occur in red and white blood cells than in plasma, but it also permeates into all body fluids and crosses the placenta. It has a biological half-life of about 5 days and is excreted only very slowly in the urine and faeces.

Mepacrine hydrochloride was bound to serum proteins *in vitro*.— G. A. Lutty, *Toxic. appl. Pharmac.*, 1978, *44*, 225.

Uses. Mepacrine was formerly widely used for the suppression and treatment of malaria but it has been superseded for these purposes by chloroquine and other more recently introduced antimalarials. Doses ranged from 100 mg daily for suppression and from 900 mg reducing to 300 mg daily for treatment. Mepacrine hydrochloride is used in the treatment of giardiasis; 100 mg thrice daily for 7 days is usually effective, though relapses may occur. A suggested dose for children is 2.7 mg per kg body-weight thrice daily.

It has been used for the expulsion of tapeworms; 100 mg is given at intervals of 5 minutes until a total dose of 1 g is reached.

Instillations of mepacrine hydrochloride or mesylate are used in the symptomatic treatment of neoplastic effusions in the pleura or peritoneum but the treatment is associated with a high frequency of toxic effects.

For the use of mepacrine as an anthelmintic, see A. Davis, *Drug Treatment in Intestinal Helminthiases*, Geneva, World Health Organization, 1973.

Giardiasis. Mepacrine 100 mg thrice daily for 5 to 7 days was usually effective in the treatment of giardiasis, although a second course might be required. The dose for children under 4 years old was one-quarter of the adult dose.— *Br. med. J.*, 1974, *2*, 347.

A 95% cure-rate was obtained in giardiasis after treatment with mepacrine hydrochloride 100 mg thrice daily for 7 days. Dosages in children were: under 1 year, 33 mg thrice daily; 1 to 4 years, 50 mg twice daily; 4 to 8 years, 50 mg thrice daily; over 8 years, 100 mg thrice daily, all for 7 days.— M. S. Wolfe, *J. Am. med. Ass.*, 1975, *233*, 1362.

Further references: G. T. Moore *et al.*, *New Engl. J. Med.*, 1969, *281*, 402; *Med. Lett.*, 1976, *18*, 39; R. E. Raizman, *Am. J. dig. Dis.*, 1976, *21*, 1070.

Malignant effusions. The value of local instillations of mepacrine in controlling effusions in advanced disseminated neoplastic disease was studied in 60 patients. For pleural effusions, an initial dose of 50 to 100 mg was followed by 200 to 400 mg daily for 4 or 5 days; patients with ascites received 100 to 200 mg followed by 400 to 800 mg daily for 3 to 5 days. The mepacrine was dissolved in 10 ml of the effusion fluid which was then re-injected. Of 33 patients clinically evaluated for 2 months or more, objective control of the effusion was maintained in 27 for 2 to 26 months. Fever, often accompanied by leucocytosis and persisting for a few hours to 10 days after completion of treatment, was noted in about half the patients.— J. E. Ultmann *et al.*, *Cancer*, 1963, *16*, 283.

Thirteen patients with neoplastic effusions were treated with mepacrine hydrochloride in doses of 100 to 200 mg daily by local instillations for pleural effusions, and 200 to 400 mg daily for ascites, usually for 3 to 5 days. Clinical benefit with favourable objective changes in all measurable criteria of the disease was seen in 9 patients for periods of up to 27 months. Mild local toxicity was frequent but haematopoietic depression did not occur. No consistent cytolytic changes of tumour cells were observed and response was attributed to the inflammation and fibrosis produced.— M. R. Dollinger *et al.*, *Ann. intern. Med.*, 1967, *66*, 249.

There was a response in 8 of 12 patients with malignant pleural effusions given mepacrine by instillation in small daily doses, and in 19 of 27 given mepacrine as a single dose through a thoracostomy tube. More disturbing and serious toxicity occurred in the second group.— E. R Borja and R. P. Pugh, *Cancer*, 1973, *31*, 899.

A beneficial effect (less than 500 ml fluid drawn at each pleurocentesis in 3 months) was achieved on 9 of 14 occasions after the instillation of mepacrine (100, 200, and 200 mg respectively on 3 occasions in 1 week), on 4 of 15 occasions after thiotepa (20 mg per instillation), and on 1 of 9 occasions after pleurocentesis alone. Fever and chest pain were limiting factors; mepacrine was suitable if the patient's condition and prognosis was good; otherwise thiotepa or pleurocentesis were preferred.— J. Mejer *et al.*, *Scand. J. resp. Dis.*, 1977, *58*, 319.

Further references: J. A. Hickman and M. C. Jones, *Thorax*, 1970, *25*, 226; M. Lee and D. A. Boyes, *J. Obstet. Gynaec. Br. Commonw.*, 1971, *78*, 843.

Pneumothorax. A patient with cystic fibrosis was treated for pneumothorax on the left side by the instillation of mepacrine hydrochloride 100 mg in 15 ml saline into the intrapleural space on 4 consecutive days. This procedure was repeated 12 months later for pneumothorax on the right. There was no recurrence of pneumothorax on either side before the patient died 11 months after the second treatment after several relapses of chronic pulmonary disease.— J. Kattwinkel *et al.*, *J. Am. med Ass.*, 1973, *226*, 557. See also R. E. Jones and S. T Giammona, *Am. J. Dis. Child.*, 1976, *130*, 777.

Tubal occlusion. Two to 4 ml of a 30% aqueous suspension of mepacrine hydrochloride instilled transvaginally once in the immediate postmenstrual phase of 2 consecutive cycles induced tubal occlusion in 93% of 134 women.— Advances in Methods of Fertility Regulation, *Tech. Rep. Ser. Wld Hlth Org. No. 527*, 1973.

Sixty women desiring sterilisation were treated by the application, by cannula within the uterus, of 1 g of mepacrine hydrochloride suspended in 7 ml of sterile water. Of 52 available for examination 4 months later, 22 had bilateral tubal patency and 3 unilateral patency; a further 6 were pregnant. The low success-rate of a single application indicated limited usefulness.— C Israngkun *et al.*, *Contraception*, 1976, *14*, 75.

Warts. A local injection technique was used in the treatment of warts in children. A 4% solution of mepacrine, in doses of 0.1 to 0.2 ml, was injected into the healthy skin at the base of the wart, 3 to 6 warts being treated at each session. The injections were repeated twice if no response followed the first injection. The treatment was successful in 97 of 112 patients. It sometimes caused slight transient pain.— A. I. Lopatin, *Pediatriya*, 1966, *45*, 71, per *Abstr. Wld Med.*, 1966, *40*, 446.

Preparations

Mepacrine Tablets *(B.P.)*. Tablets containing mepacrine hydrochloride. Protect from light.

Quinacrine Hydrochloride Tablets *(U.S.P.)*. Tablets containing mepacrine hydrochloride. Store in airtight containers.

Proprietary Names

Atabrine *(Winthrop, Canad.)*; Atabrine Hydrochloride *(Winthrop, USA)*.

Mepacrine hydrochloride was formerly marketed in certain countries under the proprietary name Quinacrine (*May & Baker*).

1383-q

Mepacrine Mesylate. Mepacrine Methanesulphonate *(B.P.C. 1963)*.

$C_{23}H_{30}ClN_3O,2CH_3SO_3H,H_2O = 610.2$.

CAS — 316-05-2 (anhydrous)

Bright yellow odourless crystals with a bitter taste. Mepacrine mesylate 120 mg is approximately equivalent to 100 mg of mepacrine hydrochloride. **Soluble** 1 in 3 of water and 1 in 36 of alcohol. A 2% solution in water has a pH of 3 to 5. **Protect** from light. Solutions should not be heated, or stored for any length of time.

Uses. Mepacrine mesylate has actions similar to those of mepacrine hydrochloride, but as it is more soluble than the hydrochloride it has been administered by intramuscular injection in the treatment of severe malaria. A dose of 360 mg has been given in 2 to 4 ml of Water for Injections.

It is given by intrapleural or intraperitoneal instillation in the treatment of neoplastic effusions.

Preparations

Mepacrine Methanesulphonate Injection *(B.P.C. 1963)*. Mepacrine Mesylate Injection. A sterile solution of mepacrine mesylate in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in Water for Injections.

Mepacrine mesylate was formerly marketed in certain countries under the proprietary name Quinacrine Soluble (*May & Baker*).

1384-p

Pamaquin *(B.P. 1953)*. Gametocidum; Pamachin; Pamaquine Embonate. Plasmoquinum, SN 971 8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline 4,4'-methylenebis(3-hydroxy-2-naphthoate).

$C_{43}H_{41}N_3O_7 = 703.8$.

CAS — 491-92-9 (base); 635-05-2 (embonate).

A yellow to orange-yellow odourless powder with a bitter taste. Practically **insoluble** in water; soluble 1 in 20 of alcohol.

Uses. Pamaquin was formerly used in the treatment of malaria but has been superseded by primaquine phosphate.

A. INGREDIENT NAME:

SULFADIMETHOXINE

B. Chemical Name:

(2,6-dimethoxy-pyrimidin-4-yl)sulphailamide

C. Common Name:

Arg.-Lenterap, Denm.-Suloplan, Ital.-Bensulfa,Chemiosalfa, Crozinal, Deltin, Diasulfa, Diazinol, Dimetossilinia, Fultamid, Ipersulfa, Levisul, Micromega, Neosulfamyd, Redifal, Risulpir, Ritarsulfa, Sulfabon, Sulfadomus, Sulfaduran, Sulfastop, Sulfomikron,Tempodiazina, Pol.- Madroxine,S. Afr.- Jatsulph, Lensulpha, Pansulph, Sulfathox, Spain-Dimetoxan, Oxazina,Sulf-reten.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay (tit.) 99%

E. Information about how the ingredient is supplied:

White Crystals from Dilute Alcohol

F. Information about recognition of the substance in foreign pharmacopeias:

Indian Pharmacopeia
British Pharmacopeia 1988
British Pharmacopeia 1993, VOL I

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Weinstein, L. A review of sulphadimethoxine. *New Engl. J. Med.* 1960; 263:842.

Vree, T. B. Pharmacokinetics. N1-glucuronidation and N4-acetylation of sulfadimethoxine in man. *Pharm. Weebl. (Sci)*, 1990;12:51-59.

Marusich, W. L., Ogrinz E.f., and Hecht. B. Safety of Sulfadimmethoxine in turkeys *Poultry Science,* 1971;50(2):513-517.

Marusich, W. L., Ogrinz, E., and Brand, M. Safety and compatibility of Sulfadimethoxine in chickens. *Poultry Science,* 1969;48(1):210-216.

Maestrone, G., Thompson, E., and Yeisley, H. Rofenaid at a 0.02% dose level in feed was effective prophylactically and therapeutically against an experimentally induced Escherichia coli airsac. The activit of Rofenaid compared very favorable with that of the aproved dose level of NF-180. *Avian Diseases,* 1979;23(3): 682-687.

Porapnev, F. V.and Skuratovich, A. A. Sulfamonomethoxin and Sulfadimethoxin in patients. *Antibiotiki.* 1973;18(5): 453-456.

Ames, T. R., Casagranda, C. L.,a nd Werdin, R.E. Effect of sulfadimethoxine-ormetoprim in the treatment of calves with induced Pasteurella pneumonia. *American Journal of Veterinary Research,* 1987;48(1): 17-20.

H. Information about dosage forms used:

Tablets

I. Information about strength:

500mg

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 201-203°
Storage stabilities (decay half-lives at -20° C) 567 days
Stable in fortified chicken liver and thigh muscle tissues during frozen storage for 1 year at -20 and -70 °C.

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-7821
51176

S0359
Lot# GF01
CAS# 122-11-2

Sulfadimethoxine

Appearance:	White crystalline powder
Melting Point:	199°C
Assay(tit.):	99% D
Solubility:	Clear (0.5/20, acetone)

JAPAN

6/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: SULFADIMETHOXINE

MANUFACTURE LOT NO.: 98F0349

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP _/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE CRYSTALS FROM DILUTE ALCOHOL. E

2) SOLUBILITY.:
SOLUBLE IN DILUTE HCL AND IN AQUEOUS SOLUTIONS OF SODIUM CARBONATE. SOLUBLE IN WARM WATER.

K **3) MELTING POINT.:**
MELTS AT ABOUT 201-203 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: S7007 NAME: SULFADIMETHOXINE

CAS #: 122-11-2

MF: C12H14N4O4S

SYNONYMS

ABCID * AGRIBON * ALBON * 4-AMINO-N-(2,6-DIMETHOXY-4-PYRIMIDINYL)

BENZENESULFONAMIDE * ARNOSULFAN * BACTROVET *
BENZENESULFONAMIDE, 4-
AMINO-N-(2,6-DIMETHOXY-4-PYRIMIDINYL)- (9CI) * DEPOSUL * DIASULFA *
DIASULFYL * DIMETAZINA *
2,6-DIMETHOXY-4-(P-AMINOBENZENESULFONAMIDO)
PYRIMIDINE * N(SUP 1)-(2,6-DIMETHOXY-4-PYRIMIDINYL)SULFANILAMIDE *

DIMETHOXYSULFADIAZINE * 2,4-DIMETHOXY-6-SULFANILAMIDO-1,3-DIAZINE *
2,
6-DIMETHOXY-4-SULFANILAMIDOPYRIMIDINE * DINOSOL * DORISUL * FUXAL *

MADRIBON * MADRIGID * MADRIQID * MADROXIN * MADROXINE * MAXULVET
*
MEMCOZINE * METOXIDON * NEOSTREPAL * OMNIBON * PERSULFEN *
RADONIN *
REDIFAL * ROSCOSULF * SCANDISIL * SDM * SDMO * SUDINE * SULDIXINE *
SULFADIMETHOXIN * SULFADIMETHOXINE * SULFADIMETHOXYDIAZINE *

SULFADIMETOSSINA (ITALIAN) * SULFADIMETOXIN * 6-SULFANILAMIDO-2,4-

DIMETHOXYPYRIMIDINE * SULFASOL * SULFASTOP * SULFOPLAN *
SULPHADIMETHOXINE * SULXIN * SYMBIO * THERACANZAN *

---------- TOXICITY HAZARDS ----------

RTECS NO: WO9030000

SULFANILAMIDE, N(SUP 1)-(2,6-DIMETHOXY-4-PYRIMIDINYL)-

TOXICITY DATA

ORL-RAT LD50:>20 GM/KG	NIIRDN 6,386,82
ORL-MUS LD50:>10 GM/KG	ARZNAD 15,1441,65
IPR-MUS LD50:866 MG/KG	NIIRDN 6,386,82
SCU-MUS LD50:791 MG/KG	NIIRDN 6,386,82
IVN-MUS LD50:844 MG/KG	NIIRDN 6,386,82
ORL-DOG LD50:>3200 MG/KG	NIIRDN 6,386,82
ORL-RBT LD50:>1 GM/KG	NIIRDN 6,386,82
IVN-RBT LD50:1000 MG/KG	NIIRDN 6,386,82

REVIEWS, STANDARDS, AND REGULATIONS

NOES 1983: HZD X2763; NIS 1; TNF 403; NOS 5; TNE 4029; TFE 2015

TARGET ORGAN DATA

VASCULAR (BP LOWERING NOT CHARACTERIZED IN AUTONOMIC SECTION)

SPECIFIC DEVELOPMENTAL ABNORMALITIES (CRANIOFACIAL)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)
DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
CAUSES EYE AND SKIN IRRITATION.
MATERIAL IS IRRITATING TO MUCOUS MEMBRANES AND UPPER RESPIRATORY TRACT.
MAY CAUSE ALLERGIC SKIN REACTION.
TARGET ORGAN(S):
BLOOD
KIDNEYS
LIVER

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

SOLID.

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

INCOMPATIBILITIES

STRONG OXIDIZING AGENTS

MAY DISCOLOR ON EXPOSURE TO LIGHT.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

TOXIC FUMES OF:

CARBON MONOXIDE, CARBON DIOXIDE

NITROGEN OXIDES

SULFUR OXIDES

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.

HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.

MAY CAUSE SENSITIZATION BY SKIN CONTACT.

IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF

WATER AND SEEK MEDICAL ADVICE.

WEAR SUITABLE PROTECTIVE CLOTHING.

DO NOT BREATHE DUST.

TARGET ORGAN(S):

BLOOD

KIDNEYS

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL

NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

...75 ml. water to 5 ml. *Dose.* Sulphadiazine, 150 to ... mg per kg body-weight daily in four 6-hourly doses.

...adiazine Tablets *(B.P.).* Tablets containing sulphad... Protect from light.

Proprietary Preparations

...adiazine Sodium *(May & Baker, UK).* Available as ...jection containing the equivalent of 250 mg of sul...diazine per ml, in ampoules of 4 ml. (Also available ... Sulphadiazine Sodium in *Austral.*).

Other Proprietary Names of Sulphadiazine

...diazine *(Belg., Fr.);* Diazyl Dulcet, S-Diazine (both *Austral.*).

832-r

Sulphadimethoxine. Sulfadimethoxine; Sol...dimetossina; Solfadimetossipirimidina. N^1-...6-Dimethoxypyrimidin-4-yl)sulphanilamide.
$C_{12}H_{14}N_4O_4S = 310.3$.

CAS — 122-11-2.

Pharmacopoeias. In *Br., Fr., It., Jug.,* and *Nord.*

A white, or creamy white, almost odourless, ...steless, crystalline powder. M.p. 198° to 204°. ...ry slightly **soluble** in water; soluble 1 in 200 of ...cohol, 1 in 800 of chloroform, and 1 in 2000 of ...ether; soluble in dilute mineral acids and in solu...ions of alkali hydroxides and carbonates. **Protect** ...from light.

...dverse Effects, Treatment, and Precautions. As ...for Sulphonamides, p.1457.

...If side-effects occur, sulphadimethoxine has the ...disadvantage that several days are required for ...its elimination from the body. The Stevens-John...son syndrome has been reported following the use ...of sulphadimethoxine.

...ffects on the blood. Sulphadimethoxine has been ...reported to cause haemolysis in patients with haemoglo...bin Zürich (an unstable haemoglobin).— E. Beutler, *Pharmac. Rev.*, 1969, *21*, 73.

...epatitis. A patient developed granulomatous reactions ...in the liver and lymph nodes, with fever, skin rash, ...jaundice, and interstitial pneumonitis, 2 days after the ...administration of 2 g of sulphadimethoxine by mouth. ...He made a full spontaneous recovery within 3 weeks.— C. R. Espiritu *et al., J. Am. med. Ass.*, 1967, *202*, 985.

...nteractions. For the effect of sulphadimethoxine in ...reducing protein binding of sulphonylurea compounds, ...see Chlorpropamide, p.853.

...For the possible effect of sulphadimethoxine on the ...half-life of tolbutamide, see Tolbutamide, p.860.

...bsorption and Fate. As for Sulphonamides, ...p.1458.

...Sulphadimethoxine is readily absorbed from the ...gastro-intestinal tract. After a single dose of 2 g ...peak blood concentrations are reached in 4 to 6 ...hours; concentrations after 24 hours are still at ...least half the original value. About 90% of sul...phadimethoxine is bound to plasma albumin. ...About 10% of sulphadimethoxine in the blood is ...present as the acetyl derivative and rather less as ...the glucuronide. Penetration into the cerebrospi...nal fluid is poor.

...Sulphadimethoxine is excreted slowly in the ...urine, about half of a single dose being recovered ...in 48 hours; about 80% is excreted in the form of ...a relatively highly soluble glucuronide, and about ...15% as the acetyl derivative. Sulphadimethoxine ...and its acetyl derivative are poorly soluble in ...urine.

...The biological half-life of sulphadimethoxine is variously ...reported as 20.2 to 41 hours.— W. A. Ritschel, *Drug Intell. & clin. Pharm.*, 1970, *4*, 332.

...Sulphadimethoxine was about 73.2% bound to human ...muscle tissue *in vitro*.— B. Fichtl and H. Kurz, *Eur. J. clin. Pharmac.*, 1978, *14*, 335.

...Uses. Sulphadimethoxine is a long-acting sulpho...namide, with the general properties of sulpho...namides, p.1458. With usual doses the blood con...centration of unconjugated sulphadimethoxine ...can be maintained at 50 to 100 μg per ml.

...The initial dose is 1 or 2 g, according to the severity of the infection, followed by a dose of 0.5 to 1 g daily. A suggested dose for children is 30 mg per kg body-weight initially, followed by one-half this amount daily.

A review of sulphadimethoxine.— L. Weinstein *et al., New Engl. J. Med.*, 1960, *263*, 842.

Leprosy. For an opinion that sulphadimethoxine is not suitable for the treatment of leprosy, see Sulphamethoxypyridazine, p.1480.

For earlier clinical reports on sulphadimethoxine, see Martindale 27th Edn, p. 1478.

Preparations

Sulphadimethoxine Tablets *(B.P.).* Tablets containing sulphadimethoxine. Protect from light.

Madribon *(Roche, UK).* Sulphadimethoxine, available as scored tablets of 500 mg. (Also available as Madribon in *Austral., Belg., Canad., Denm., Fr., Ger., Ital., S.Afr., Spain, Swed., Switz.*).

Other Proprietary Names

Arg.—Lenterap; *Denm.*—Sulfoplan; *Ital.*—Bensulfa, Chemiosalfa, Crozinal, Deltin, Diasulfa, Diazinol, Dimetossilina, Fultamid, Ipersulfa, Levisul, Micromega, Neosulfamyd, Redifal, Risulpir, Ritarsulfa, Sulfabon, Sulfadomus, Sulfaduran, Sulfastop, Sulfomikron, Tempodiazina; *Pol.*—Madroxine; *S.Afr.*—Jatsulph, Lensulpha, Pansulph, Sulfathox; *Spain*— Dimetoxan, Oxazina, Sulf-reten.

4933-f

Sulphadimidine *(B.P., B.P. Vet., Eur. P.).* Sulphadimid.; Sulfadimidine; Sulfadimidinum; Sulphadimethylpyrimidine; Sulphamethazine; Sulfamethazine *(U.S.P.);* Sulfadimérazine; Sulfadimezinum; Solfametazina. N^1-(4,6-Dimethylpyrimidin-2-yl)sulphanilamide.
$C_{12}H_{14}N_4O_2S = 278.3$.

CAS — 57-68-1.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulphasomidine (see p.1483). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Arg., Aust., Br., Chin., Cz., Eur., Fr., Ger., Hung., Ind., Int., It., Jug., Neth., Nord., Pol., Roum., Rus., Swiss, Turk.,* and *U.S.*

White or yellowish-white, odourless or almost odourless, crystals or powder with a slighlty bitter taste. M.p. 197° to 200°. It darkens and decomposes on exposure to light.

Very slightly **soluble** in water; soluble 1 in 200 of boiling water; soluble 1 in 120 of alcohol, 1 in 30 of acetone, 1 in 600 of chloroform, and 1 in 2500 of ether; soluble in dilute mineral acids and in aqueous solutions of alkali hydroxides and carbonates.

Sulphadimidine may be **sterilised** by reducing to a fine powder, drying at 100°, and heating in the final sealed containers so that the whole of the powder is maintained at 150° for 1 hour; the sterilised powder is not more than slightly discoloured. **Store** in airtight containers. Protect from light.

The effect of formulation and compression on the absorption of sulphadimidine tablets.— M. C. B. van Oudtshoorn *et al., J. Pharm. Pharmac.*, 1971, *23*, 583.

Mention of changes in dissolution-rate and equilibrium solubility of the hydrophobic drug sulphadimidine, brought about by the presence of hydrophilic polymers, povidone and carmellose sodium, in the dissolution medium.— *Pharm. J.*, 1978, *2*, 249.

A study on the formulation and evaluation of a sulphadimidine suspension for infants.— R. N. Nasipuri and E. O. Ogunlana, *Pharm. J.*, 1978, *2*, 258.

4934-d

Sulphadimidine Sodium *(B.P., B.P. Vet.).* Sulphadimid. Sod.; Sulfadimidine Sodium; Soluble Sulphadimidine; Soluble Sulphamethazine; Soluble Sulphadimethylpyrimidine.
$C_{12}H_{13}N_4NaO_2S = 300.3$.

CAS — 1981-58-4.

Pharmacopoeias. In *Aust., Br., Ind., Pol.,* and *Turk.*

White or creamy-white, odourless or almost odourless, hygroscopic crystals or powder with a bitter alkaline taste. It slowly discolours and decomposes on exposure to light; on exposure to air it absorbs carbon dioxide and becomes less soluble in water. Sulphadimidine sodium 1.08 g is approximately equivalent to 1 g of sulphadimidine.

Soluble 1 in 2.5 of water and 1 in 60 of alcohol. A 10% solution has a pH of 10 to 11. Solutions are most stable at pH 10 to 11; precipitation of sulphadimidine occurs below pH 10. Solutions are **sterilised** by distributing into ampoules, replacing the air with nitrogen or other suitable gas, sealing, and autoclaving, or by filtration into sterile ampoules in which the air is replaced by nitrogen or other suitable gas. **Incompatible** with acids, iron salts, and salts of heavy metals. **Store** in airtight containers. Protect from light.

Incompatibility. A haze developed over 3 hours when sulphadimidine sodium was mixed with amiphenazole hydrochloride in sodium chloride injection. An immediate precipitate occurred with chlorpromazine hydrochloride, promazine hydrochloride, promethazine hydrochloride, and a yellow colour with a precipitate developing over 3 hours occurred with hydralazine hydrochloride in dextrose injection or sodium chloride injection. An immediate precipitate occurred when sulphadimidine sodium was mixed with prochlorperazine mesylate in sodium chloride injection, but when they were mixed in dextrose injection a haze developed over 3 hours.— B. B. Riley, *J. Hosp. Pharm.*, 1970, *28*, 228.

Adverse Effects, Treatment, and Precautions. As for Sulphonamides, p.1457.

The Stevens-Johnson syndrome has been reported after treatment with sulphadimidine. Sulphadimidine and its acetyl derivative are relatively soluble in urine; the risk of crystalluria is therefore slight, but adequate fluid intake is recommended.

Sulphadimidine sodium should not be given intrathecally or subcutaneously; intramuscular injections are painful.

Effects on the blood. A 7-year-old boy developed acute haemolytic anaemia following a total dose of 28 g of sulphadimidine given over a period of 5 days. Recovery occurred after treatment with blood transfusion, prednisone, and penicillin intramuscularly. Hypersensitivity rather than a direct haemolytic action was thought to be the cause.— J. L. Grech and E. A. Cachia, *Br. med. J.*, 1959, *2*, 1309.

Effects on the heart. A 12-year-old African boy developed a fulminating skin lesion 2 days after sulphadimidine therapy (6 g in 2 days) and acute cardiomyopathy 28 days later. The cardiomyopathy was considered most likely to be a hypersensitivity reaction to sulphadimidine.— E. T. M. MacSearraigh and K. M. Patel, *Br. med. J.*, 1968, *3*, 33.

Solubility in urine. The solubilities of sulphadimidine and its acetyl derivative in urine at 37° were 692 and 670 μg per ml respectively at pH 6, 752 and 864 μg per ml at pH 6.4, 833 and 907 μg per ml at 6.8, 997 and 1140 μg per ml at pH 7.2, 1.445 and 1.762 mg per ml at pH 7.6, and 1.793 and 2.16 mg per ml at pH 8.— L. H. Schmidt *et al., J. Pharmac. exp. Ther.*, 1944, *81*, 17.

Absorption and Fate. As for Sulphonamides, p.1458.

Sulphadimidine is readily absorbed from the gastro-intestinal tract and about 60 to 80% is bound to plasma albumin. It penetrates into the cerebrospinal fluid, but less readily than sulphadiazine; concentrations of sulphadimidine in body fluids may be more than half those in the blood. About 40% of sulphadimidine in the blood is present as the acetyl derivative. About 50% of a dose may be excreted in the urine in 2 days, 70% being in the form of the acetyl derivative.

A study of the kinetics of the intestinal absorption of sulphadimidine.— G. L. Turco *et al., Clin. Pharmac. Ther.*, 1966, *7*, 603.

Sulphadimidine tablets, 50% of which dissolved in 1 to 5 minutes *in vitro*, were given to 9 subjects in a 3-g dose, and gave average serum concentrations of free plus acetylated sulphadimidine at 0.5, 1, 4, 10, and 24 hours

Antimicrobial Action
As for Sulphamethoxazole, p.281.

Pharmacokinetics
Sulphadiazine is readily absorbed from the gastrointestinal tract, peak blood concentrations being reached 3 to 6 hours after a single dose; 20 to 55% has been reported to be bound to plasma proteins. It penetrates into the cerebrospinal fluid to produce therapeutic concentrations, which may be more than half of those in the blood, within 4 hours of administration by mouth. Up to 40% of sulphadiazine in the blood is present as the acetyl derivative.

About 50% of a single dose of sulphadiazine given by mouth is excreted in the urine in 24 hours; 15 to 40% is excreted as the acetyl derivative.

The urinary excretion of sulphadiazine and the acetyl derivative is dependent on pH. About 30% is excreted unchanged in both fast and slow acetylators when the urine is acidic whereas about 75% is excreted unchanged by slow acetylators when the urine is alkaline. The half-life of sulphadiazine ranges from 7 to 12 hours and that of its metabolite from 8 to 12 hours.[1]

1. Vree TB, *et al.* Determination of the acetylator phenotype and pharmacokinetics of some sulphonamides in man. *Clin Pharmacokinet* 1980; 5: 274–94.

Uses and Administration
Sulphadiazine is a short-acting sulphonamide which has been used similarly to sulphamethoxazole (see p.282) in the treatment of infections due to susceptible organisms. It has been used in the treatment of nocardiosis and lymphogranuloma venereum, and has been given for the prophylaxis of rheumatic fever in penicillin-allergic patients. For details of these infections and their treatment see Choice of Antibiotic, p.133. Sulphadiazine is also given with pyrimethamine for the treatment of toxoplasmosis (see p.612).

In the treatment of susceptible infections sulphadiazine may be given by mouth in usual doses of 2 to 4 g followed by up to 6 g daily in divided doses, although up to 8 g daily has been suggested for toxoplasmosis; a suggested dose in children is 75 mg per kg body-weight initially then 150 mg per kg daily in divided doses to a maximum of 6 g daily. A concentration in the blood of 100 to 150 µg per mL is desirable. For the prophylaxis of rheumatic fever, patients weighing less than about 30 kg are given 500 mg once daily, while those over 30 kg may receive 1 g once daily.

Sulphadiazine is also given intravenously as the sodium salt. The usual dose is the equivalent of sulphadiazine 2 to 3 g initially, followed by 1 g four times daily for 2 days; subsequent treatment is given by mouth. Children over 2 months of age may be given the equivalent of 50 mg per kg initially, followed by 25 mg per kg four times daily.

Intravenous doses of sulphadiazine sodium are given by infusion or by slow intravenous injection of a solution containing up to 5%. It may be diluted with sodium chloride 0.9% injection. Sulphadiazine sodium has been given by deep intramuscular injection but great care must be exercised to prevent damage to subcutaneous tissues and the intravenous route is preferred.

For the use of sulphadiazine with trimethoprim, see Co-trimazine, p.217. Sulphadiazine has also been given in association with other sulphonamides, particularly sulfamerazine and sulphadimidine, to reduce the problems of low solubility in urine.

Preparations
Names of preparations are listed below; details are given in Part 3.

Official Preparations
BP 1993: Sulphadiazine Injection;
USP 23: Sulfadiazine Sodium Injection; Sulfadiazine Tablets; Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Proprietary Preparations
Fr.: Adiazine.

Multi-ingredient preparations. *Aust.:* Bisolvonamid; Ophcil-N; Rhinon; Triglobe; Urospasmon sine phenazopyridino; *Belg.:* Trimatrim; *Canad.:* Coptin; Ovoquinol†; Trisulfaminic; *Fr.:* Antrima; *Ger.:* Bisolvonamid†; Diben-amid†; Nitrofurantoin comp.†; Sagittamid†; Spasmo-Urocleart†; Sterinor; Sulfa-Ozothin†; Sulfa-Uro-Tablinen†; Sulfa-Urolong†; sulfopecticept†; Triglobe; Uroclear; Urospasmon; Urospasmon sine; *Ital.:* Chemiovis†; Geomix†; Kombinax; Oxosint; Sterinor; Sulfadrina†; Tibirox; *S.Afr.:* Tersulpha†; Trisulpha†; *Spain:* Bio Hubber; Bio Hubber Fuerte; Bio Hubber Simple†; Bronco Aseptilex; Broncomicin Bals†; Triglobe; *Swed.:* Trimin sulfa; *Switz.:* Urospasmon; *USA:* Neotrizine†; Triple Sulfa No. 2.

The symbol † denotes a preparation no longer actively marketed

Sulphadimethoxine (4932-r)
Sulphadimethoxine *(BAN).*

Solfadimetossina; Solfadimetossipirimidina; Sulfadimethoxine *(rINN).* N^1-(2,6-Dimethoxypyrimidin-4-yl)sulphanilamide.

$C_{12}H_{14}N_4O_4S$ = 310.3.

CAS — 122-11-2.

Pharmacopoeias. In *Fr.* and *It.*

Sulphadimethoxine is a long-acting sulphonamide with properties similar to those of sulphamethoxazole (see p.280). It is readily absorbed from the gastro-intestinal tract, and about 98 to 99% is bound to plasma proteins. Half-lives of about 30 to 40 hours have been reported.

The initial dose is 1 or 2 g, according to the severity of the infection, followed by a dose of 0.5 to 1 g daily.

Pharmacokinetics. A study of the pharmacokinetics of sulphadimethoxine and its metabolites.[1]

1. Vree TB, *et al.* Pharmacokinetics, N1-glucuronidation and N4-acetylation of sulfadimethoxine in man. *Pharm Weekbl (Sci)* 1990; 12: 51–9.

Preparations
Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
Ital.: Chemiosalfa†; Deltin†; Risulpir†; Ritarsulfa†; Sulfadren†; Sulfastop†; *S.Afr.:* Sulfathox†.

Sulphadimidine (4933-f)
Sulphadimidine *(BAN).*

Solfametazina; Sulfadimerazine; Sulfadimezinum; Sulfadimidine *(rINN);* Sulfadimidinum; Sulfamethazine; Sulphadimethylpyrimidine; Sulphamethazine. N^1-(4,6-Dimethylpyrimidin-2-yl)sulphanilamide.

$C_{12}H_{14}N_4O_2S$ = 278.3.

CAS — 57-68-1.

NOTE. Sulfadimethylpyrimidine has been used as a synonym for sulphasomidine (p.283). Care should be taken to avoid confusion between the two compounds, which are isomeric.

Pharmacopoeias. In *Aust., Belg., Br., Chin., Cz., Eur., Fr., Ger., Hung., Int., It., Neth., Port., Swiss,* and *US.*

The standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

White or yellowish-white, almost odourless, crystals or powder. It darkens on exposure to light.

Very slightly **soluble** in water; soluble in acetone; slightly soluble in alcohol; very slightly soluble to practically insoluble in ether; it dissolves in dilute mineral acids and in aqueous solutions of alkali hydroxides. **Protect** from light.

Sulphadimidine Sodium (4934-d)
Sulphadimidine Sodium *(BANM).*

Soluble Sulphadimidine; Sulfadimidine Sodium; Sulfamethazine Sodium.

$C_{12}H_{13}N_4NaO_2S$ = 300.3.

CAS — 1981-58-4.

Pharmacopoeias. In *Aust., Br., Cz.,* and *Int.*

White or creamy-white, odourless or almost odourless, hygroscopic crystals or powder. 1.08 g of monograph substance is approximately equivalent to 1 g of sulphadimidine.

Freely **soluble** in water; sparingly soluble in alcohol. A 10% solution has a pH of 10 to 11. **Protect** from light.

Sulphadimidine is a short-acting sulphonamide with similar properties to those of sulphamethoxazole (see p.280).

It is well absorbed from the gastro-intestinal tract and about 80 to 90% has been stated to be bound to plasma protein. Reported half-lives have ranged from 1.5 to 4 hours in fast and 5.5 to 8.8 hours in slow acetylators. Because of the relatively high solubility of the drug and its acetyl metabolite crystalluria may be less likely than with sulphamethoxazole.

In the treatment of susceptible infections sulphadimidine has been given by intravenous or deep intramuscular injection as the sodium salt, in usual doses of 3 g initially, followed by 1.5 g every 6 hours. Children may be given 0.5 to 2.5 g initially, depending on age, followed by half the initial dose every 6 hours. Sulphadimidine has been given in similar doses by mouth.

Sulphadimidine has also been used with trimethoprim similarly to co-trimoxazole (p.219) and in association with other sulphonamides, particularly sulfamerazine and sulphadiazine.

Because its pharmacokinetics differ in fast and slow acetylators, sulphadimidine has been used to determine acetylator status.

Preparations
Names of preparations are listed below; details are given in Part 3.

Official Preparations
BP 1993: Paediatric Sulphadimidine Oral Suspension; Sulphadimidine Injection; Sulphadimidine Tablets;
USP 23: Trisulfapyrimidines Oral Suspension; Trisulfapyrimidines Tablets.

Proprietary Preparations
Eire: Sulphamezathine; *UK:* Sulphamezathine†.

Multi-ingredient preparations. *Canad.:* Trisulfaminic; *S.Afr.:* Tersulpha†; *USA:* Neotrizine†; Triple Sulfa No. 2.

Sulphafurazole (4936-h)
Sulphafurazole *(BAN).*

Sulfafurazole *(pINN);* Sulfafurazolum; Sulfisoxazole; Sulphafuraz. N^1-(3,4-Dimethylisoxazol-5-yl)sulphanilamide.

$C_{11}H_{13}N_3O_3S$ = 267.3.

CAS — 127-69-5.

Pharmacopoeias. In *Br., Cz., Fr., Ger., It., Jpn, Neth., Port., Swiss,* and *US.*

A white or yellowish-white, odourless crystalline powder or crystals.

Soluble 1 in 7700 of water, 1 in 10 of boiling alcohol; sparingly soluble in alcohol; slightly soluble in dichloromethane and in ether; it dissolves in solutions of alkali hydroxides and in dilute mineral acids. **Store** in airtight containers. Protect from light.

Acetyl Sulphafurazole (4937-m)
Sulfisoxazole Acetyl. N^1-Acetyl Sulphafurazole; *N*-(3,4-Dimethylisoxazol-5-yl)-*N*-sulphanilylacetamide.

$C_{13}H_{15}N_3O_4S$ = 309.3.

CAS — 80-74-0.

NOTE. Acetyl sulphafurazole is to be distinguished from the N^4-acetyl derivative formed from sulphafurazole by conjugation in the body.

Compounded preparations of erythromycin ethyl succinate (erythromycin ethylsuccinate) and acetyl sulphafurazole (sulfisoxazole acetyl) in USP 23 may be represented by the name Co-erynsulfisox.

Pharmacopoeias. In *US.*

A white to slightly yellow crystalline powder. 1.16 g of monograph substance is approximately equivalent to 1 g of sulphafurazole.

Practically **insoluble** in water; soluble 1 in about 180 of alcohol, 1 in 35 of chloroform, 1 in about 200 of methyl alcohol, and 1 in about 1100 of ether. **Store** in airtight containers. Protect from light.

Sulphafurazole Diethanolamine (4938-b)
NU-445; Sulfafurazole Diolamine *(pINNM);* Sulfisoxazole Diolamine *(USAN);* Sulphafurazole Diolamine. The 2,2′-iminobisethanol salt of sulphafurazole.

$C_{11}H_{13}N_3O_3S.C_4H_{11}NO_2$ = 372.4.

CAS — 4299-60-9.

Pharmacopoeias. In *US.*

An odourless, white to off-white, fine, crystalline powder. 1.39 g of monograph substance is approximately equivalent to 1 g of sulphafurazole.

Soluble 1 in 2 of water, 1 in 16 of alcohol, 1 in 1000 of chloroform, 1 in 4 of methyl alcohol, and 1 in 250 of isopropyl alcohol; practically insoluble in ether. **Store** in airtight containers. Protect from light.

the sublimate with a glass rod and mix it in a test-tube with 1 ml of a 5 per cent w/v solution of *resorcinol* in *alcohol*. Add 1 ml of *sulphuric acid* and mix by shaking; a deep red colour appears at once. Cautiously dilute the mixture with 25 ml of ice-cold *water* and add an excess of *dilute ammonia solution*; a blue or reddish-blue colour is produced.

(E) It melts at about 255° with decomposition, Appendix 5.11.

Clarity and colour of solution : A solution of 1.0 g in a mixture of 10 ml of *N sodium hydroxide* and 15 ml of *water* is clear and the colour is not more intense than that of 25 ml of mixture of 1.45 ml of *ferric chloride C.S.*, 0.03 ml of *cobalt chloride C.S.*, 0.03 ml of *copper sulphate C.S.* and sufficient *water* to produce 100.0 ml.

Acidity : Heat 1.0 g with 50 ml of *carbon dioxide-free water* at about 70° for five minutes, cool quickly to 20° and filter; titrate 25 ml of the filtrate to pH 7.0 with *0.1N sodium hydroxide*; not more than 0.1 ml of *0.1N sodium hydroxide* is required.

Heavy metals : Not more than 20 parts per million, determined on 1.0 g by Method B, Appendix 3.2.4.

Chloride : 1 g dissolved by warming in 5 ml of *nitric acid* and 5 ml of *water*, complies with the *limit test for chlorides*, Appendix 3.2.2.

Sulphate : 1 g dissolved by warming in 5 ml of *hydrochloric acid* and 5 ml of *water*, complies with the *limit test for sulphates*, Appendix 3.2.8.

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g drying in an oven at 105°, Appendix 5.8.

Assay : Carry out the **Assay** described under Succinylsulphathiazole. Each ml of *0.1M sodium nitrite* is equivalent to 0.02503 g of $C_{10}H_{10}N_4O_2S$.

Storage : Store in well-closed, light-resistant containers.

Sulphadiazine Tablets

Category : Antibacterial.

Dose : Sulphadiazine, initial dose, 3 g; subsequent doses upto 4 g daily, in divided doses.

Usual strength : 0.5 g.

Standards : Sulphadiazine Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Sulphadiazine, $C_{10}H_{10}N_4O_2S$.

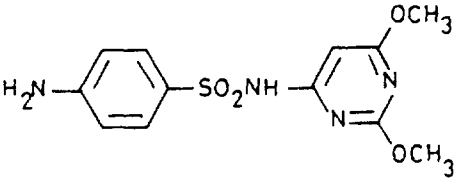
Identification : (A) Triturate a quantity of the powdered tablets, equivalent to about 0.5 g of Sulphadiazine, with two successive quantities of 5 ml of *chloroform* and reject the chloroform. Triturate the residue with 10 ml of *dilute ammonia solution* for five minutes, add 10 ml of *water* and filter. Warm the filtrate until most of the ammonia is expelled, cool, and acidify with *acetic acid*. Collect the precipitate, wash with *water*, and dry at about 100°; the residue has a melting range between 252° and 256°; Appendix 5.11 and complies with **Identification** tests (A) to (D) described under Sulphadiazine.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.5 g of Sulphadiazine and dissolve as completely as possible in a mixture of 50 ml of *water* and 10 ml of *hydrochloric acid*. Carry out the *nitrite titration*, Appendix 3.3.4. Each ml of *0.1M sodium nitrite* is equivalent to 0.02503 g of $C_{10}H_{10}N_4O_2S$.

Storage : Store in well-closed, light-resistant containers.

Sulphadimethoxine



$C_{12}H_{14}N_4O_4S$ Mol. Wt. 310.33

Category : Antibacterial.

Dose : Initial dose, 1 to 2 g; subsequent doses, 500 mg daily.

Description : White or creamy-white, crystalline powder; almost odourless; tasteless.

Solubility : Very slightly soluble in *water*; slightly soluble in *alcohol*; soluble in dilute mineral acids and in solutions of alkali hydroxides and carbonates.

Standards : Sulphadimethoxine is N^1-(2,6-dimethoxypyrimidin-4-yl) sulphanilamide. It contains not less than 99.0 per cent of $C_{12}H_{14}N_4O_4S$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths

as, and have similar relative intensities to, those in the spectrum of *sulphadimethoxine R.S.*, Appendix 5.15 B.

(B) Dissolve about 0.1 g in 3 ml of *sodium hydroxide solution* and 50 ml of *water* and dilute to 100 ml with *water*. To 5 ml add 100 mg of *phenol*, and heat to boiling. Cool, add 0.5 ml of *sodium hypochlorite solution* and a few drops of *sodium hydroxide solution*; a yellow colour is produced.

(C) It gives the reactions of *primary aromatic amines*, Appendix 3.1, giving an orange-red precipitate

(D) Suspend about 20 mg in 5 ml of *water* and add *sodium hydroxide solution* until completely dissolved. Add a few drops of *copper sulphate solution*; the solution turns yellow, and a yellow precipitate is formed.

Melting range : Between 197° and 204°, Appendix 5.11.

Related substances : Carry out the method for *thin-layer chromatography*, Appendix 5.4.3, using *silica gel H* as the coating substance and a mixture of 20 volumes of *chloroform*, 2 volumes of *methyl alcohol* and 1 volume of *dimethylformamide*, as the mobile phase. Apply separately to the plate 10 µl of each two solutions in a mixture of 9 volumes of *alcohol* and 1 volume of *strong ammonia solution* containing (1) 0.25 per cent w/v of the substance being examined and (2) 0.00125 per cent w/v of *sulphanilamide R.S.* After removal of the plate, allow it to dry in air and spray with a 10 per cent v/v solution of *sulphuric acid* in *alcohol*, heat at 105° for 30 minutes, and immediately expose to nitrous fumes in a closed glass tank for 15 minutes [nitrous fumes may be generated by adding *sulphuric acid (50 per cent w/w)* dropwise to a solution containing 10 per cent w/v of *sodium nitrite* and 3 per cent w/v of *potassium iodide*]. Place the plate in a current of warm air for 15 minutes and spray with a 0.5 per cent w/v solution of *N-(1-naphthyl) ethylenediamine hydrochloride* in *alcohol*. If necessary, allow to dry and repeat the spraying. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

Heavy metals : Not more than 20 parts per million, determined by Method A on a solution prepared by dissolving 1 g in 5 ml of *sodium hydroxide solution* and 20 ml of *water*, Appendix 3.2.4.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Assay : Weigh accurately about 0.5 g and carry out the *nitrite titration*, Appendix 3.3.4. Each ml of *0.1M sodium nitrite* is equivalent to 0.03103 g of $C_{12}H_{14}N_4O_4S$.

Storage : Store in well-closed, light-resistant containers.

Sulphadimethoxine Tablets

Category : Antibacterial.

Dose : Sulphadimethoxine; initial dose, 1 to 2 g; subsequent doses 500 mg daily.

Usual strength : 500 mg.

Standards : Sulphadimethoxine Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Sulphadimethoxine, $C_{12}H_{14}N_4O_4S$.

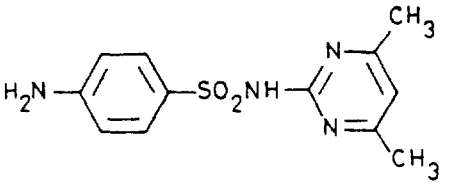
Identification : Triturate a quantity of the powdered tablets equivalent to 0.5 g of Sulphadimethoxine with 5 ml of *0.5N hydrochloric acid*; filter, and neutralise the filtrate to *litmus paper* with *0.5N sodium hydroxide*. The precipitate after washing with *water* and drying at 105°, melts at about 201°, Appendix 5.11, and complies with the **Identification** tests described under Sulphadimethoxine.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.5 g of Sulphadimethoxine and carry out the *nitrite titration*, Appendix 3.3.4. Each ml of *0.1M sodium nitrite* is equivalent to 0.03103 g of $C_{12}H_{14}N_4O_4S$.

Storage : Store in light-resistant containers.

Sulphadimidine



$C_{12}H_{14}N_4O_2S$ Mol. Wt. 278.32

Category : Antibacterial.

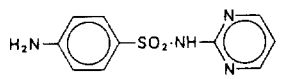
Dose : In the treatment of systemic infections; initial dose, 3 g; subsequently upto 6 g daily, in divided doses.

In the treatment of urinary tract infection; initial dose, 2 g; subsequently upto 4 g in divided doses.

Description : White or creamy-white crystals or crystalline powder; almost odourless; taste, bitter.

Solubility : Very slightly soluble in *water*; soluble in *acetone*, in mineral acids, in alkalis and in alkaline

Sulphadiazine ☆



$C_{10}H_{10}N_4O_2S$ 250.3 *68-35-9*

Sulphadiazine is N^1-(pyrimidin-2-yl)sulphanilamide. It contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{10}H_{10}N_4O_2S$, calculated with reference to the dried substance.

Characteristics White, yellowish-white or pinkish-white crystals or crystalline powder. It melts at about 255°, with decomposition.

Solubility Practically insoluble in *water* and in *chloroform*; very slightly soluble in *ethanol (96%)*; slightly soluble in *acetone*. It dissolves in aqueous solutions of alkali hydroxides and in dilute mineral acids.

Identification *Test A may be omitted if tests B, C and D are carried out. Tests C and D may be omitted if tests A and B are carried out.*

A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the spectrum of *sulfadiazine EPCRS*.

B. In the test for Related substances, the principal spot in the chromatogram obtained with solution (2) corresponds in position and size to the principal spot in the chromatogram obtained with solution (4).

C. Heat 3 g in a test-tube inclined at an angle of 45° with the lower part immersed in a silicone oil-bath at about 270°. It decomposes and a white or yellowish-white sublimate is produced. The *melting point* of the sublimate, after recrystallisation from *toluene* and drying at 100°, is 123° to 127°, Appendix V A, Method I.

D. Dissolve 5 mg in 10 ml of 1M *hydrochloric acid* and dilute 1 ml of this solution to 10 ml with *water*. The solution, without further acidification, yields the *reaction* characteristic of primary aromatic amines, Appendix VI.

Acidity Heat 1.25 g of the finely powdered substance at 70° with 25 ml of *carbon dioxide-free water* for 5 minutes. Cool for about 15 minutes in ice and filter. To 20 ml of the filtrate add 0.1 ml of *bromothymol blue solution*. Not more than 0.2 ml of 0.1M *sodium hydroxide VS* is required to change the colour of the solution.

Colour of solution Dissolve 0.8 g in 10 ml of 1M *sodium hydroxide*. The solution is not more intensely coloured than *reference solution* Y_5, BY_5 or GY_5, Appendix IV B, Method II.

Heavy metals 1.0 g complies with *limit test D for heavy metals*, Appendix VII (20 ppm). Use 2 ml of *lead standard solution (10 ppm Pb)* to prepare the standard.

Related substances Complies with test C for *related substances in sulphonamides*, Appendix III A.

Loss on drying When dried to constant weight at 100° to 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulphated ash Not more than 0.1%, Appendix IX A, Method II. Use 1 g.

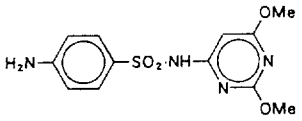
Assay Dissolve 0.2 g in a mixture of 20 ml of 2M *hydrochloric acid* and 50 ml of *water*. Add 3 g of *potassium bromide*, cool in ice and carry out the method for *amperometric titration*, Appendix VIII B. Each ml of 0.1M *sodium nitrite VS* is equivalent to 0.02503 g of $C_{10}H_{10}N_4O_2S$.

Storage Sulphadiazine should be kept in a well-closed container and protected from light.

Preparation
Sulphadiazine Injection

Action and use Antibacterial.

Sulphadimethoxine



$C_{12}H_{14}N_4O_4S$ 310.3 *122-11-2*

Sulphadimethoxine is N^1-(2,6-dimethoxypyrimidin-4-yl)sulphanilamide. It contains not less than 99.0 per cent and not more than 101.0 per cent of $C_{12}H_{14}N_4O_4S$, calculated with reference to the dried substance.

Characteristics A white or creamy-white, crystalline powder; odourless or almost odourless.

Solubility Very slightly soluble in *water*; slightly soluble in *ethanol (96%)*. It dissolves in dilute mineral acids and in aqueous solutions of alkali hydroxides and carbonates.

Identification A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of sulphadimethoxine.

B. Yields the *reaction* characteristic of primary aromatic amines, Appendix VI, producing an orange-red precipitate.

Acidity Heat 1 g with 50 ml of *carbon dioxide-free water* at about 70° for 5 minutes, cool quickly to 20° and filter. 25 ml of the filtrate requires not more than 0.1 ml of 0.1M *sodium hydroxide VS* for titration to pH 7.0, Appendix V L.

Clarity and colour of solution A 5.0% w/v solution in 2M *hydrochloric acid* is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* BY_5, Appendix IV B, Method I.

Melting point 198° to 204°, Appendix V A.

Heavy metals 1.0 g complies with *limit test C for heavy metals*, Appendix VII (20 ppm). Use 2 ml of *lead standard solution (10 ppm Pb)* to prepare the standard.

Related substances Complies with test B for *related substances in sulphonamides*, Appendix III A.

Loss on drying When dried to constant weight at 100° to 105°, loses not more than 0.5% of its weight. Use 1 g.

Sulphated ash Not more than 0.1%, Appendix IX A.

Assay Dissolve 0.5 g in a mixture of 75 ml of *water* and 10 ml of *hydrochloric acid* and carry out the method for *amperometric titration*, Appendix VIII B. Each ml of 0.1M *sodium nitrite VS* is equivalent to 0.03103 g of $C_{12}H_{14}N_4O_4S$.

Storage Sulphadimethoxine should be protected from light.

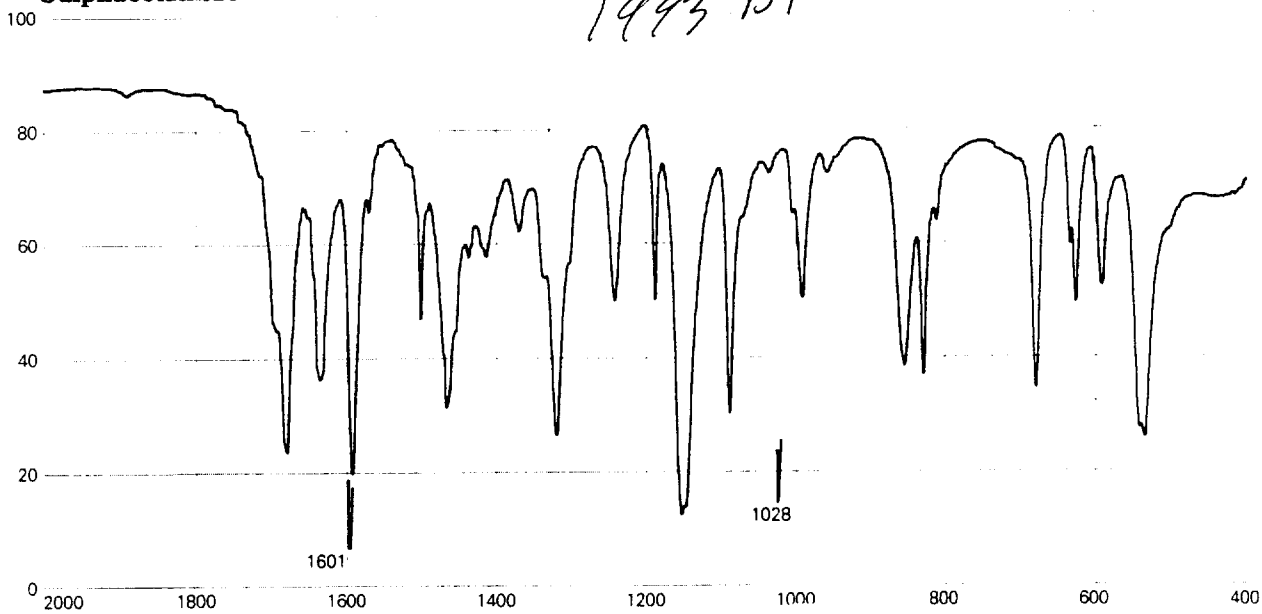
Preparation
Sulphadimethoxine Tablets

Action and use Antibacterial.

1993 BP Vol A

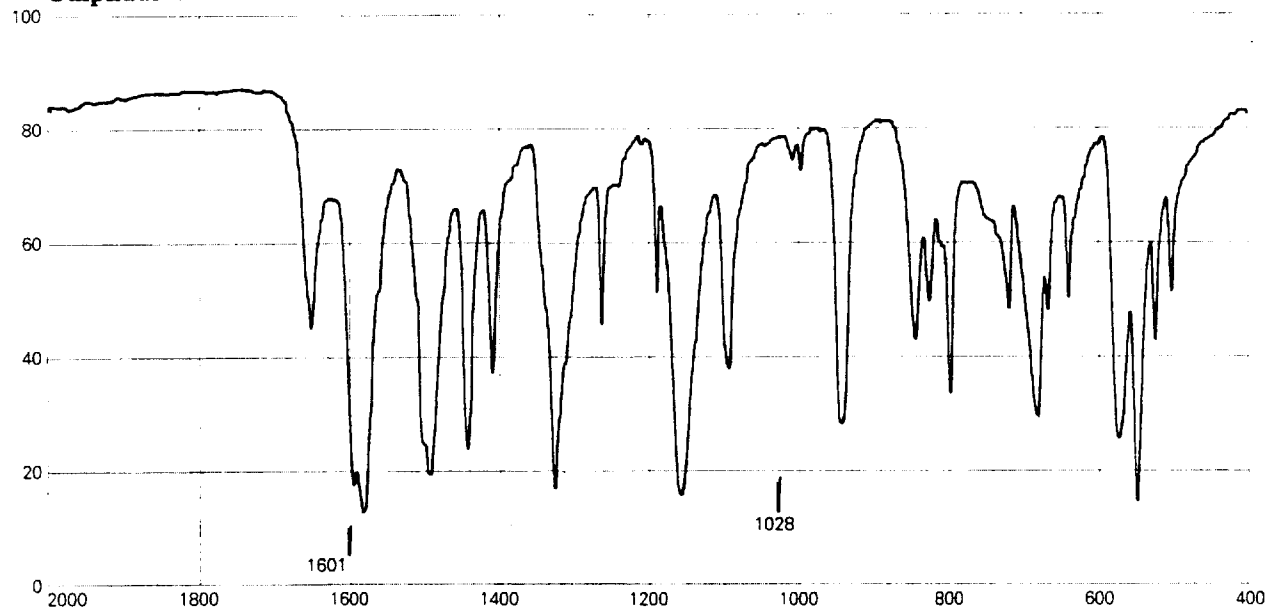
Sulphacetamide

Phase: Potassium bromide disc



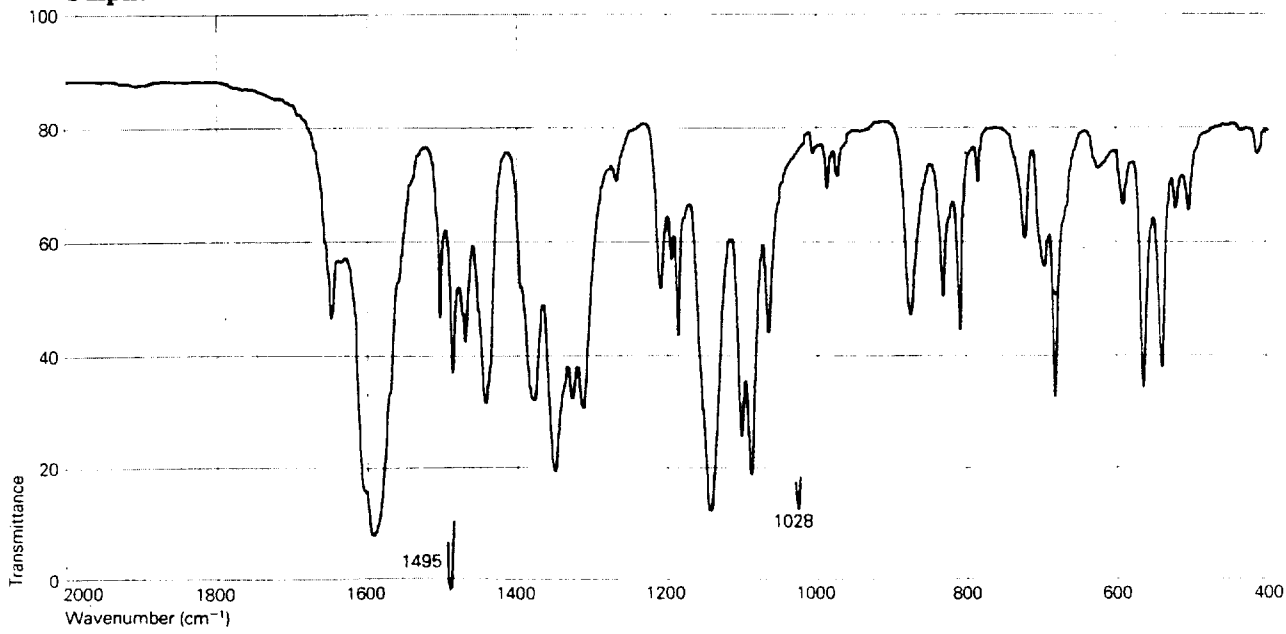
Sulphadiazine

Phase: Potassium bromide disc



Sulphadimethoxine

Phase: Potassium bromide disc



Database: Medline <1966 to present>

Set	Search	Results
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2	(safety and efficacy).tw.	14057
3	1 and 2	0
4	stability.tw.	54760
5	1 and 4	3
6	(safety and efficacy).ti,ab,sh.	14168
7	1 and 6	0
8	from 5 keep 1-3	3
9	safety.tw.	44957
10	efficacy.tw.	108250
11	1 and 9	4
12	1 and 10	8
13	from 11 keep 1-2	2
14	from 12 keep 1-6,8	7

<1>
Unique Identifier
97466138
Authors
Thomas GK. Millar RG. Anstis PW.
Title
Stability of sulfonamide antibiotics in spiked pig liver tissue during frozen storage.
Source
Journal of AOAC International. 80(5):988-95, 1997 Sep-Oct.
Abstract
A bulk portion of homogenized pig liver tissue was spiked at room temperature with 0.2 mg/kg (twice the Australian maximum residue limit) of each of sulfathiazole, sulfachlorpyridazine, sulfadimidine (sulfamethazine), sulfaquinoxaline, and sulfadimethoxine. After subsampling and packaging, selected individual packaged units were tested to confirm homogeneity of the prepared material. The material was stored frozen at -20 degrees C and analyzed in replicate by liquid chromatography on 11 sampling dates over a period of about 6 months. Analytical data were plotted on a log-linear scale and subjected to linear regression on the basis of first-order kinetics for the decay. Storage stabilities (decay half-lives at -20 degrees C) calculated from the mean slope of regression lines were sulfadimethoxine, 567 days; sulfadimidine, 457 days; sulfachlorpyridazine, 312 days; sulfathiazole, 291 days;

and sulfaquinoxaline, 271 days. Significant depletion (65% loss) of residue was observed for sulfaquinoxaline during preparation of spiked bulk liver tissue. An extension of the study to measure the storage stability of sulfaquinoxaline under accelerated decay conditions (refrigerator temperature, 4 degrees C) showed it to be relatively unstable, with a decay half-life of 11 days. Results demonstrate the need for both regulatory agencies and testing laboratories to be aware of potential errors associated with improper transport, storage, and handling of tissue samples submitted for antibiotic testing.

<2>
Unique Identifier
70107926
Authors
Reimerdes EH. Seydel JK.
Title
[Significance of acid stability of sulfonamides for the determination of their N4-metabolites]. [German]
Source
Arzneimittel-Forschung. 19(11):1863-8, 1969 Nov.

<3>
Unique Identifier
94257994
Authors
Parks OW.
Title
Stability of sulfaquinoxaline, sulfadimethoxine, and their N4-acetyl derivatives in chicken tissues during frozen storage.
Source
Journal of AOAC International. 77(2):486-8, 1994 Mar-Apr.
Abstract
The N4-acetyl derivatives of sulfaquinoxaline and sulfadimethoxine were stable in fortified chicken liver and thigh muscle tissues during frozen storage for 1 year at -20 and -70 degrees C. In contrast, the parent compounds depleted approximately 35% in liver tissues at -20 degrees C. The transformation of the depleted sulfa drugs to their N4-glucopyranosyl derivatives was negligible, suggesting that products other than glucosides resulted during the storage period.

Database: Medline <1966 to present>

Set	Search	Results
1	exp sulfadimethoxine/	448
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3	1 and 2	0
4	stability.tw.	54760
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6	(safety and efficacy).ti,ab,sh.	14168
7	1 and 6	0
8	from 5 keep 1-3	3
9	safety.tw.	44957
10	efficacy.tw.	108250
11	1 and 9	4
12	1 and 10	8
13	from 11 keep 1-2	2
14	from 12 keep 1-6,8	7

<1>
Unique Identifier
71191828
Authors
Marusich WL. Ogrinz EF. Hecht B. Mitrovic M.
Title
Safety of sulfadimethoxine potentiated mixture (Rofenaid), a new broad spectrum coccidiostat-antibacterial, in turkeys.
Source
Poultry Science. 50(2):512-7, 1971 Mar.

<2>
Unique Identifier
70050587
Authors
Marusich WL. Ogrinz E. Brand M. Mitrovic M.
Title
Safety and compatibility of sulfadimethoxine potentiated mixture (Ro 5-0013), a new broad spectrum coccidiostat-antibacterial, in chickens.
Source
Poultry Science. 48(1):210-6, 1969 Jan.

Database: Medline <1966 to present>

Set	Search	Results
1	exp sulfadimethoxine/	448
2	(safety and efficacy).tw.	14057
3	1 and 2	0
4	stability.tw.	54760
5	1 and 4	3
6	(safety and efficacy).ti,ab,sh.	14168
7	1 and 6	0
8	from 5 keep 1-3	3
9	safety.tw.	44957
10	efficacy.tw.	108250
11	1 and 9	4
12	1 and 10	8
13	from 11 keep 1-2	2
14	from 12 keep 1-6,8	7

<1>
Unique Identifier
79250686
Authors
Gates NL. Rich JE. Myers LL. Harp JA.
Title
Efficacy of selected antimicrobial agents in treating diarrheal disease in neonatal lambs.
Source
Veterinary Medicine, Small Animal Clinician. 74(5):707-9, 1979 May.

<2>
Unique Identifier
80108976
Authors
Maestrone G. Thompson E. Yeisley H. Mitrovic M.
Title
Prophylactic and therapeutic activity of Rofenaid-40A in an experimental Escherichia coli airsac infection in chickens.
Source
Avian Diseases. 23(3):682-7, 1979 Jul-Sep.
Abstract
Rofenaid at a 0.02% dose level in feed was effective prophylactically and therapeutically against an experimentally induced Escherichia coli airsac infection in

chickens. The activity of Rofenaid compared very favorably with that of the approved dose level of NF-180. Furthermore, the prophylactic use of Rofenaid did not interfere with the therapeutic efficacy of NF-180.

<3>
Unique Identifier
74110196
Authors
Potapnev FV. Skuratovich AA.
Title
[Comparative evaluation of therapeutic efficacy of sulfamonomethoxin and sulfadimethoxin in patients with gonorrhea]. [Russian]
Source
Antibiotiki. 18(5):453-6, 1973 May.

<4>
Unique Identifier
74084351
Authors
Mitrovic M. Schildknecht EG.
Title
Comparative chemotherapeutic efficacy of Agribon (sulfadimethoxine) and other agents against coccidiosis in chickens and turkeys.
Source
Poultry Science. 52(4):1253-60, 1973 Jul.

<5>
Unique Identifier
72113377
Authors
Mitrovic M. Bauernfeind JC.
Title
Efficacy of sulfadimethoxine in turkey diseases.
Source
Avian Diseases. 15(4):884-93, 1971 Oct-Dec.

<6>
Unique Identifier
72003749
Authors
Orton CT. Hambly LR.
Title

Efficacy studies on potentiated sulfadimethoxine as a chicken coccidiostat.
Source
Poultry Science. 50(5):1341-6, 1971 Sep.

<7>
Unique Identifier
87154648
Authors
Ames TR. Casagranda CL. Werdin RE. Hanson LJ.
Title
Effect of sulfadimethoxine-ormetoprim in the treatment of calves with induced Pasteurella pneumonia.
Source
American Journal of Veterinary Research. 48(1):17-20, 1987 Jan.
Abstract
The efficacy of sulfadimethoxine (SDM)-ormetoprim (OMP) was evaluated in calves with induced Pasteurella pneumonia. A dose-titration study comparing 3 doses of SDM-OMP was performed to determine the optimal dose. Treatments included: group 1--nontreated controls; group 2--33 mg of SDM-OMP/kg of body weight, orally on day 1 and 17 mg/kg on days 2 to 5; group 3--66 mg of SDM-OMP/kg, orally on day 1 and 33 mg/kg on days 2 to 5; group 4--99 mg of SDM-OMP/kg, orally on day 1 and 50 mg/kg on days 2 to 5; and group 5--11 mg of oxytetracycline/kg, IV daily for 4 days. Group-2 calves responded to treatment as well as did group-5 calves. Group-4 calves responded the same as did group-3 calves. However, group-2 calves did not respond as well as did groups 3, 4, and 5 calves.

Safety of Sulfadimethoxine Potentiated Mixture (Rofenaid®),* a New Broad Spectrum Coccidiostat-Antibacterial, in Turkeys

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Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

(Received for publication August 31, 1970)

INTRODUCTION

ROFENAID® is a new broad spectrum coccidiostat and antibacterial containing sulfadimethoxine (N'-[2, 6-dimethoxy-4-pyrimidinyl] sulfanilamide) potentiated with ormetoprim (2, 4-diamino-5-[4, 5-dimethoxy-2-methylbenzyl] pyrimidine) in a ratio of 5:3. Sulfadimethoxine alone has been shown to be highly effective, therapeutically, against all pathogenic species of coccidia in chickens (0.05%) and turkeys (0.025%) when administered in the drinking water (Mitrovic and Bauernfeind, 1967) and efficacious in the prevention of turkey coccidiosis at 0.0125% in the feed (Mitrovic, 1968). Mitrovic (1967) reported that sulfadimethoxine was also effective in the therapy of fowl cholera in chickens (0.05%) and turkeys (0.025%) and infectious coryza in chickens (0.05%) when administered in the drinking water. The combination of sulfadimethoxine and the potentiator ormetoprim, a folic acid antagonist, in a 5:3 ratio results in enhanced broad spectrum coccidiostatic and antibacterial activity when fed continuously to broilers at 0.02% and replacement birds at 0.01% (Mitrovic *et al.*, 1969 a, b). Similarly, the same combination is highly effective as a broad spectrum coccidiostat and antibacterial when fed continuously to turkeys at 0.01% (Mitrovic *et al.*, 1971 a, b). Previous investigators had reported on several folic acid antagonists acting to synergize the coccidiostatic properties of sulfonamides (Lux, 1954; Joyner and Kendall, 1955, 1956; Horton-Smith *et al.*, 1960; Ball, 1964, and Clarke, 1962, 1964). The safety of sulfadimethoxine and ormetoprim alone and in the 5:3 combination has been reported for the chicken (Marusich *et al.*, 1969). The present report is concerned with the safety of the 5:3 combination in turkey broilers and breeders.

SPECIFIC EXPERIMENTAL PROCEDURES AND RESULTS

Broad Breasted White (B.B.W.) poults (sex identified) from a commercial hatchery were used for all experiments. All birds were housed in electrically-heated, thermostatically-controlled batteries with raised wire floors for the first 4 weeks, transferred to grower units with wire floors and no heat for the next 4 weeks and then moved to floor pens where necessary. All housing conditions—including floor space, lighting and temperature—in each respective study were comparable for each treatment group. A commercial-type mash free of antibiotics, arsenicals or other medication was fed in all trials. Depending on the length of the study, the following dietary regimen was followed: 28% protein starter from 0 to 8 weeks; 25% protein grower from 9 to 13 weeks; 21% protein grower from 14 to 17 weeks; 16% protein finisher from 18 to 24 weeks; and an 18% protein layer mash from 25 to 44 weeks.

LD_{50} of a Single Oral Dose. Following a preliminary range-finding experiment, 2-

* Rofenaid® is Roche's trademark for a coccidiostat and antibacterial containing sulfadimethoxine potentiated with ormetoprim.

TABLE 1. - *Summary of data from LD_{50} study with sulfadimethoxine, ormetoprim and the 5:3 combination (Rofenaid) in poults*

Treatment	mg./bird	mg./kg. body wt.	Initial wt. (g.)	Mortality	2-Week gain (g.)	Calculated $LD_{50} \pm$ S.E.
Sulfadimethoxine	80	402	199	0/10	386	1750 ± 200 mg./kg.
	160	800	200	0/10	356	
	240	1218	197	3/10	348	
	320	1616	198	4/10	340	
	400	2030	197	5/10	300	
	480	2449	196	6/10	330	
	560	2857	196	8/10	300	
Ormetoprim	20	102	197	0/10	404	400 ± 40 mg./kg.
	40	204	196	0/10	409	
	60	305	197	1/10	332	
	80	408	196	6/10	311	
	100	510	196	6/10	379	
	120	600	200	8/10	310	
	140	711	197	10/10	--	
Sulfadimethoxine-Ormetoprim combination (5:3)	60	306	196	0/10	433	930 ± 45 mg./kg.
	100	510	196	0/10	354	
	140	718	195	1/10	371	
	180	905	199	4/10	329	
	220	1128	195	8/10	310	
	300	1538	195	10/10	—	

week-old poults were assembled into uniform groups of 10 each (5 females + 5 males), based on body weight. Graded levels of sulfadimethoxine, ormetoprim and the combination of the 2 drugs in the 5:3 ratio were administered as a single oral dose in gelatin sleeve-type capsules to groups of 10 poults each.

The results are summarized in Table 1. Based on the method of Miller and Tainter (1944), the following LD_{50} values were calculated: sulfadimethoxine (1750 mg./kg. ± 200 mg./kg.), ormetoprim (400 mg./kg. ± 40 mg./kg.) and the 5:3 combination (930 mg./kg. ± 45 mg./kg.).

The onset of toxicity is rather slow and varies with the specific drug. Clinical signs are not well defined. Birds appear lethargic with wings drooped; they rest on their hocks and do not attempt to eat or drink. Time of death varies with sulfadimethoxine from 24 to 96 hours with the majority dying during the latter 3 days. With ormetoprim, death occurs rapidly, generally within the first 24 hours with a few deaths up to 48 hours. The 5:3 combination is variable with deaths occurring in less than 24 hours and up to 96 hours. All surviving birds recover rather rapidly and subsequently show essentially normal growth (Table 1).

All birds that died were necropsied and the following gross pathological lesions observed with sulfadimethoxine: hepatonephromegaly, catarrhal enteritis; with ormetoprim: hepatonephromegaly; with the combination: hepatonephromegaly, edematous small intestine and catarrhal enteritis.

13-WEEK SAFETY TRIAL WITH SULFADIMETHOXINE-ORMETOPRIM 5:3 COMBINATION

Two-day-old poults were assembled into 24 groups of 10 each (5 females + 5 males), based on body weight. Levels of 0, 0.01, 0.03 and 0.05% of the 5:3 combination of sulfadimethoxine + ormetoprim were fed continuously to 6 replicates of 10 birds over a 13-week period. All turkeys

TABLE 2.—*Performance of turkeys fed graded levels of sulfadimethoxine-ormetoprim combination (5:3) for 13 weeks*

% Drug	Gain (kg.)	% Gain	Feed intake (g.)	Feed conversion	Rofenaid intake			Mortality
					Total (mg.)	Average daily (mg.)	Average daily (mg./kg.)	
0 to 4-Week Data								
0	0.518	100	787	1.52	—	—	—	2/60
0.01	0.520	100.4	800	1.54	80.0	2.9	9.2	3/60
0.03	0.520	100.4	785	1.51	235.5	8.4	26.7	0/60
0.05	0.510	98.5	795	1.56	397.5	14.2	45.8	3/60
0 to 8-Week Data								
0	2.068	100	3469	1.68		—	—	2/60
0.01	2.173	105.1	3604	1.66	360.4	6.4	5.6	3/60
0.03	2.164	104.6	3582	1.66	1074.6	19.2	16.9	0/60
0.05	2.231	107.9	3678	1.65	1839.0	32.8	28.0	3/60
0 to 13-Week Data								
0	4.224	100	9906	2.35	—	—		2/60
0.01	4.545	107.6**	10502	2.31	1050.2	11.5	5.0	3/60
0.03	4.474	105.9**	10304	2.30	3091.2	34.0	14.8	0/60
0.05	4.565	108.1**	10680	2.34	5340.0	58.7	25.1	4/60

* Average weight of 2-day-old poults was 55 g.
** Statistically significant at $P < .05$ (2-sided test).

were weighed as groups at 4 weeks and individually at 8 and 13 weeks. Feed consumption data were recorded over the entire 13-week period. Hematological data were obtained on 10 representative birds (5 females + 5 males) from each treatment group at 13 weeks. Gross pathological observations were made on these same birds selected for hematology. Selected organs including liver, kidneys, spleen, heart and thyroid were weighed and related to body weight. Tissue portions were taken from 15 organs of 6 controls and 6 birds fed 0.05% drug and preserved in neutral buffered 10% formalin for histological examination.

Growth, feed conversion and mortality data in relation to drug level and drug intake are summarized in Table 2 after 4, 8 and 13 weeks' continuous feeding. No adverse effects were seen in the performance of turkeys with any drug level. Body weights at 13 weeks were significantly better ($P < 0.05$) for each drug level fed, compared with the nonmedicated controls.

Hematological data, including hemoglobin, hematocrit, R.B.C. and differential are shown as averages for the 10 turkeys per treatment group in Table 3 with no differences seen which can be associated solely with drug level fed.

Postmortem examination of all vital organs from 10 turkeys per treatment group after 13 weeks on test revealed no abnormal gross lesions which could be attributed to drug treatment. The weight of selected organs and their weight as a percent of body weight are shown in Table 4 as averages for the 10 birds per treatment. The data show the normal variability to be expected in turkeys of this age.

Sections of brain, liver, kidney, lung, heart, thyroid, pituitary, sciatic nerve, adrenal, gonads, bone marrow, pancreas, spleen, small and large intestine tissue from

TABLE 3.—*Hematology* on turkeys after 13 weeks' feeding of graded levels of sulfadimethoxine-ormetoprim combination (5:3)*

% Drug	Hemoglobin g./100 ml.	Hematocrit—% vol. R.B.C.	RBC X10⁶	Differential cell count—% N.S.N.**	Heterophils	Lymphocytes	Monocytes	Eosinophils	Basophils
0	9.62	34.4	2.33	0.2	48.2	44.2	1.4	1.8	4.4
0.01	9.13	35.6	2.38	0.1	48.1	47.4	2.4	0.4	1.4
0.03	9.43	35.4	2.53	0.7	49.9	45.7	3.3	0.0	0.4
0.05	9.16	35.2	2.41	0.1	52.4	43.0	1.3	1.2	1.0

* Average for 10 turkeys (5 females+5 males).
** Non-segmented neutrophils.

6 control turkeys (3 females + 3 males) and from 6 fed 0.05% drug showed no differences between the two groups in the occurrence or incidence of abnormal lesions, other than those abnormalities to be expected in a normal turkey population.

TURKEY BREEDER TRIAL WITH SULFADIMETHOXINE-ORMETOPRIM

B.B.W. hens and toms maintained for 35 weeks on nonmedicated feed from another study were assembled into 2 groups of 19 hens each and 2 groups of 4 toms each. Egg production was recorded for 10 days. One group (hens #1–19) laid 40 eggs and the second group (hens #20–38) laid 43 eggs. At this point, hens #1–19 (Group #1) were fed 0.05% sulfadimethoxine-ormetoprim 5:3 combination in the layer mash and hens #20–38 (Group 2) were continued on the nonmedicated layer mash. The 2 groups of toms were then separated from the hens; one group was also placed on 0.05% drug and the other fed nonmedicated feed. The hens were artificially inseminated weekly with pooled semen collected weekly from the respective 4 toms maintained on the same ration as the hens. A 15-hour light day was maintained throughout the study. A triple crossover design was used with the medicated and nonmedicated rations fed for periods of 21, 26, 27 and 30 days.

Eggs were collected 4 times daily and placed in the incubator at weekly intervals. They were candled at 9, 16 and 23 days and moved to the hatching section on the 26/27th day. Within 24 hours of hatching, all poults were placed on nonmedicated turkey starter ration, and their growth performance was recorded over a 3-week period.

Table 5 details the egg production, fertility, hatchability and poult performance for the 2 groups of hens fed the medicated and nonmedicated rations in a triple crossover design. The data show that the intermittent

TABLE 4.—*Selected organ weights of turkeys* sacrificed for gross pathology after 13 weeks' feeding of graded levels of sulfadimethoxine-ormetoprim combination (5:3)*

% Drug	Body wt. (kg.)	Liver g.	Liver %**	Kidneys g.	Kidneys %	Spleen g.	Spleen %	Heart g.	Heart %	Thyroid g.	Thyroid %
0	4.68	77.2	1.65	27.1	0.58	5.9	0.126	20.2	0.432	0.20	0.0042
0.01	5.04	78.4	1.56	27.2	0.54	5.1	0.101	21.3	0.423	0.23	0.0045
0.03	5.23	87.6	1.67	31.1	0.59	5.9	0.113	23.1	0.442	0.23	0.0043
0.05	5.17	86.7	1.68	27.0	0.52	4.8	0.093	22.3	0.431	0.23	0.0044

* Average for 10 turkeys (5 females+5 males).
** Organ weight as percent of body weight.

TABLE 5.—*Egg production, fertility, hatchability and growth of poults from turkey hens fed 0.05% sulfadimethoxine-ormetoprim combination (5:3) in a triple crossover design*

Hen no.	% Drug	No. of days	No. of hens	Total eggs	Eggs hen/day	Eggs set	Fertility no.	Fertility %	Hatchability no.	Hatchability %	Hatched poult performance 1-day wt. (g.)	Hatched poult performance 3-week gain (g.)
Intermittent Feeding Performance												
1–19	0.05	21	19	116	0.29	96	78	81	60	77	45	177
1–19	0	26	19	173	0.35	152	131	86	79	60[d]	47	187
1–19	0.05	27	19	169	0.33	149	134	90	104	78	54	191
1–19	0	30	19	166	0.29	145	127	88	107	84	54	204
20–38	0	21	19	168	0.42	139	66	47	53	80	45	190
20–38	0.05	26	18[a]	204	0.44[c]	174	115	66	60	52[d]	48	190
20–38	0	27	17[b]	153	0.33[c]	134	103	77	82	80	53	172
20–38	0.05	30	17	174	0.34	139	114	82	92	81	51	192
Combined Feeding Performance												
1–38	0.05	52	38	663	0.35[e]	558	441	79.0	316	71.7	50.0	187.5
1–38	0	52	38	660	0.35[e]	570	427	74.9	321	75.2	49.3	188.3

[a] One hen died while on 0.05% drug ration.
[b] One hen died while on control ration.
[c] Adjusted to loss of 1 hen during the specific period.
[d] Incubator shut off for 2 days.
[e] Adjusted to deaths as noted under a, b.

feeding of 0.05% sulfadimethoxine-ormetoprim 5:3 combination for from 21 to 30 days has no adverse effect on turkey breeder hens or toms, based on the several parameters cited. The data for the 38 hens were combined for the periods they received 0.05% drug (52 days) and compared to their performance while on nonmedicated feed (52 days). No difference in performance was seen between the 2 dietary regimens.

SUMMARY AND CONCLUSIONS

The toxicity and safety of Rofenaid, a new broad spectrum coccidiostat and antibacterial containing sulfadimethoxine and ormetoprim in a 5:3 ratio, was studied in turkeys. The LD_{50} of a single oral dose in 2-week-old poults was 1750 ± 200 mg./kg. for sulfadimethoxine, 400 ± 40 mg./kg. for ormetoprim and 930 ± 45 mg./kg. for the 5:3 combination.

A 13-week safety study was run with the 5:3 combination of sulfadimethoxine and ormetoprim fed at 0.01%, 0.03% and 0.05% total drug. These levels represent 1, 3 and 5 times the suggested coccidiostatic-antibacterial prophylactic use level (0.01%) for turkeys. No signs of toxicity were seen with any drug level, based on growth, feed conversion, mortality, hematology, gross pathology and histopathology. Growth was significantly increased ($P < .05$) with all drug levels.

Performance of turkey breeder hens and toms fed 0.05% drug was compared with those on nonmedicated feed in a triple crossover design for periods of 21, 26, 27 and 30 days. Rofenaid had no adverse effect on breeders, based on egg production, fertility, hatchability and performance of hatched poults.

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СРАВНИТЕЛЬНАЯ ОЦЕНКА ТЕРАПЕВТИЧЕСКОЙ ЭФФЕКТИВНОСТИ СУЛЬФАМОНОМЕТОКСИНА И СУЛЬФАДИМЕТОКСИНА У БОЛЬНЫХ ГОНОРЕЕЙ

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Sulfamonometho + Sulfadimetoxin

С появлением пенициллина и затем других антибиотиков сульфаниламидным соединениям была отведена второстепенная роль. Введение пенициллина в арсенал противогонорейных средств резко сократило сроки лечения больных, привело к значительному снижению случаев безуспешного лечения и осложнений у больных гонореей.

Однако широкое и не всегда обоснованное применение антибиотиков привело к появлению и постепенному увеличению числа штаммов гонококков с пониженной чувствительностью к пенициллину и другим антибиотикам [1—5]. Параллельно с этим наблюдается и увеличение случаев неудач при лечении больных гонореей антибиотиками [6—9].

В литературе также все чаще появляются сообщения о многообразных клинических формах лекарственной аллергии вплоть до случаев со смертельным исходом при назначении антибиотиков [10—12].

Полученные в последнее время полусинтетические пенициллины (метициллин, оксациллин, ампициллин и др.) не разрешили полностью проблемы терапии больных с антибиотикоустойчивыми формами гонореи и с непереносимостью к пенициллину, так как они могут вызывать те же аллергические реакции, что и природные пенициллины.

В связи с этим в последнее время внимание многих исследователей привлекают сульфаниламидные соединения. Высказывались предположения [13], что, поскольку сульфаниламиды в течение многих последних лет широко не применяются у больных гонореей, не исключена возможность повышения чувствительности к ним гонококков. Наблюдения показали, что норсульфазол и сульфадимезин малоэффективны при лечении больных гонореей.

Интерес к сульфаниламидным соединениям значительно повысился после получения препаратов пролонгированного действия (сульфапиридазин, сульфапиродаксин, сульфадиметоксин и др.), которые по своей эффективности превосходят прежние сульфаниламиды.

В настоящем сообщении приведены результаты изучения эффективности сульфамонометоксина и сульфадиметоксина в терапии больных гонореей.

Сульфамонометоксин (синонимы: диаметон, DS-36) и сульфадиметоксин (синонимы: мадрибон, сульксин, суперсульфа) относятся к препаратам пролонгированного действия. В СССР синтезированы во Всесоюзном научно-исследовательском химико-фармацевтическом институте (ВНИХФИ). В эксперименте на животных (мыши и кролики) максимальная концентрация сульфамонометоксина в сыворотке крови определялась через 1—4 часа после введения, держалась на высоком уровне в течение 10 часов, после чего снижалась и составляла 50% максимума [14].

Максимальная концентрация сульфадиметоксина в сыворотке крови у людей после однократного введения 1—2 *г* препарата определяется через

3—8 часов; половина принятой дозы (50%) выводится из организма с чой через 48—72 часа [15]. В отличие от других сульфаниламидных п паратов до 80% сульфадиметоксина находится в моче в виде хорошо р воримого глюкуронида, что практически исключает возможность возн новения кристаллурии [14].

В опытах на мышах сульфамонометоксин и сульфадиметоксин ока лись малотоксичными, проявляли высокую химиотерапевтическую акт ность при инфекциях, вызванных пневмококком, стрептококком, киш ной, дизентерийной и брюшнотифозной палочками [14—17]. Длитель введение сульфадиметоксина мышам не оказывало вредного действия потомство [18].

Лечение сульфамонометоксином и сульфадиметоксином проведено 153 больных (148 мужчин и 5 женщин), страдавших различными форм гонорейной инфекции. 92 больных лечили в урологическом стациона где они находились 12—17 дней и более и выписывались для дальнейш диспансерного наблюдения только после комбинированной провока и неоднократных отрицательных результатов лабораторного исследова на гонококки. Остальные больные получали лечение амбулаторно.

В возрасте до 20 лет было 11 больных, от 21 года до 30 лет — от 31 года до 40 лет — 32 и старше 40 лет — 8 больных.

Инкубационный период продолжительностью 3—4 дня был конста рован у 70 больных, от 5 до 7 дней — у 46, 10—14 дней — у 26, от 2 дель и более — у 5. У 6 человек длительность инкубационного периода тановить не удалось. С давностью заболевания до 7 дней было 34 больн от 8 до 14 дней — 36, от 2 недель до 1 месяца — 52, от 1 до 2 месяцев — и более 2 месяцев — 12.

Таким образом, более чем у половины больных (83) давность забо вания была свыше 2 недель. Это объясняется тем, что из 153 больных, торым было назначено лечение сульфамонометоксином и сульфадиметок ном, 57 ранее безуспешно лечились различными антибиотиками в дру лечебных учреждениях. У 17 из этих больных рецидив гонореи насту после лечения препаратами пенициллина (бензилпенициллин, экмоновоц лин, бициллин-3), у 11 — пенициллина и левомицетина, у 5 — пениц лина и тетрациклина, у 4 — бициллина-3, мономицина и эритромици у 3 — бициллина и мономицина, у 3 — бициллина и эритромицина, у 3 бициллина, мономицина и тетрациклина, у 5 — пенициллина и норсу фазола, у 2 — тетрациклина, у 2 — метициллина, у 1 — левомицет и у 1 больного после последовательного применения экмоновоциллина, вомицетина, олеандомицина, стрептоцида, норсульфазола и тетрацикли

У всех больных до лечения сульфамонометоксином и сульфадимет сином диагноз гонореи был подтвержден лабораторными данными.

При клиническом обследовании у 60 мужчин был диагностирован остр и подострый передний уретрит, у 59 — острый тотальный уретрит, у 1 тотальный уретрит и простатит, у 7 — тотальный уретрит и эпидидим у 2 — свежий передний торпидный уретрит и у 8 — хронический уретр У 3 женщин была хроническая гонорея и у 2 — острая гонорея нижн отдела.

Смешанная гонорейно-трихомонадная инфекция наблюдалась у 12 бо ных (10 мужчин и 2 женщины).

У 12 больных лечение сульфаниламидными препаратами провед в связи с непереносимостью антибиотиков.

Сульфамонометоксин и сульфадиметоксин назначали внутрь в в таблеток по 500 *мг*. Больные с неосложненными формами гонореи получ препарат в курсовой дозе 14—17 *г* (первые 2 дня по 1,5 *г* через каждые 8 сов и последующие дни по 1 *г* 3 раза в сутки); лицам с осложненной, жей, торпидной и хронической формами гонореи курсовую дозу увеличи ли до 20—21 *г*. Больным с торпидной и хронической формами гонореи, кр сульфаниламидов, назначали иммунотерапию (гоновакцина). Местное

чение уретры во время приема препаратов не проводили. В дни приема сульфамонометоксина и сульфадиметоксина назначали обильное щелочное питье (содовая вода, боржоми).

Больным, у которых уретрит сопровождался эпидидимитом или простатитом, для более быстрого разрешения воспалительного инфильтрата в пораженном органе одновременно с сульфаниламидами назначали аутоиммунотерапию, инъекции пирогенала, физиотерапевтические процедуры и др.

Лечение сульфамонометоксином проведено у 69 больных (64 мужчинам и 5 женщинам), при этом 35 из них препарат был назначен после безуспешного лечения различными антибиотиками и 7 — в связи с указанием на непереносимость антибиотиков. Под влиянием терапии сульфамонометоксином гонококки из отделяемого половых органов исчезли у 66 больных (в том числе у всех 35 больных, ранее безуспешно леченных различными антибиотиками). У 3 мужчин клинические симптомы заболевания (обильные выделения из уретры, диффузно мутная моча) продолжали оставаться без изменений на протяжении всего курса лечения, а при микроскопическом обследовании обнаруживались гонококки.

Сульфадиметоксин был применен у 84 мужчин, страдавших различными формами гонореи. Непосредственно после окончания терапии гонококки исчезли из отделяемого уретры у 72 больных (в том числе у 15 из 22 ранее безуспешно леченных антибиотиками). У 12 больных лечение сульфадиметоксином было безрезультатным.

Все больные после окончания лечения находились под нашим наблюдением в течение 1—8 месяцев. В этот период они подвергались неоднократным повторным клиническим и лабораторным обследованиям. Среди больных, леченных сульфамонометоксином, рецидив гонореи был установлен у 5 мужчин (у 4 больных острым уретритом через 5—11 дней после окончания терапии и у 1 больного, ранее безуспешно леченного пенициллином, через $1^1/_2$ месяца).

После терапии сульфадиметоксином ранние рецидивы заболевания были констатированы у 9 человек (в том числе у 2 ранее леченных антибиотиками).

Таким образом, стойкое этиологическое излечение (исчезновение гонококков) наступило у 61 (88,4 %) больного после терапии сульфамонометоксином (при этом у 33 из 35 безуспешно леченных антибиотиками) и у 63 (75 %) больных после назначения сульфадиметоксина (в том числе у 13 из 22 с антибиотикоустойчивыми формами гонореи).

Для изучения быстроты исчезновения гонококков под влиянием терапии сульфаниламидными препаратами продленного действия нами были проведены бактериоскопические исследования отделяемого уретры у 24 больных, леченных сульфамонометоксином и у 15 больных во время терапии сульфадиметоксином. При исследовании почасовых мазков, окрашенных по Граму, установлено, что гонококки из отделяемого уретры исчезали в течение от 8 до 48 часов после начала лечения, причем у большинства из них (36 человек) — через 16—40 часов. Заметной разницы в сроках исчезновения гонококков у больных, успешно леченных сульфамонометоксином и сульфадиметоксином, не наблюдалось.

Постгонорейные воспалительные процессы имелись у 11 больных (9 мужчин и 2 женщины), получавших лечение сульфамонометоксином, и у 16 после терапии сульфадиметоксином. У 6 из них были обнаружены влагалищные трихомонады. У 11 мужчин при уретроскопии были выявлены инфильтративные изменения в слизистой оболочке мочеиспускательного канала и у 10 — простатит.

Лечение сульфамонометоксином и сульфадиметоксином больные переносили хорошо, побочных явлений не наблюдалось. Лишь один больной во время приема сульфамонометоксина жаловался на небольшую головную боль.

Для выяснения возможного влияния препаратов на некоторые функции организма мы изучали в динамике состояние периферической крови, пигментную функцию печени и состав мочи. Исследование морфологического состава периферической крови и содержания билирубина в сыворотке крови проводили до лечения и спустя 7—10 дней после его окончания. Мочу, кроме того, исследовали во время приема препаратов. При этом отклонений от физиологической нормы не наблюдалось.

Таким образом, результаты наших исследований позволяют нам сделать вывод, что сульфамонометоксин является эффективным средством в терапии больных гонореей. Для излечения заболевания достаточно назначения его в курсовой дозе 14—17 *г* больным с неосложненными формами гонореи и в дозе 20—21 *г* при наличии осложнения со стороны придаточных половых желез, а также при торпидных и хронических формах.

Особая ценность сульфамонометоксина состоит в том, что он с успехом может быть применен у больных, которым назначение антибиотиков противопоказано.

Учитывая, что сульфадиметоксин значительно менее эффективен у больных гонореей, чем сульфамонометоксин, а также бо́льшую вероятность возникновения побочных реакций, к его назначению следует прибегать лишь в исключительных случаях.

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COMPARATIVE EVALUATION OF THERAPEUTIC EFFICACY OF SULPHAMONOMETOXIN AND SULPHADIMETOXIN IN PATIENTS WITH GONORRHEA

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Data on the treatment of 84 and 69 patients suffering from gonorrhea with sulphadimetoxin and sulphamonometoxin respectively are presented. Sulphamonometoxin was more effective than sulphadimetoxin. Sulphamonometoxin was especially active in gonorrhea cases previosly treated without any success by various antibiotics.

of antibiotic polyresistance to the El-Tor vibrions under the conditions of rapid development of the infection did not exceed 10^{-8}. Such a low rate of the transmission factor transfer may be due to rapid multiplication of the cholera vibrions in the animal intestine and unfavourable for conjugation ratios of the microbes.

Sulfa monomethoxin + Sulfadimethoxin

УДК 615.281:547.551.525.211.1].036.8:616.973

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СРАВНИТЕЛЬНАЯ ОЦЕНКА ТЕРАПЕВТИЧЕСКОЙ ЭФФЕКТИВНОСТИ СУЛЬФАМОНОМЕТОКСИНА И СУЛЬФАДИМЕТОКСИНА У БОЛЬНЫХ ГОНОРЕЕЙ

Отдел венерологии (зав.— проф. Т. В. Васильев) Центрального научно-исследовательского кожно-венерологического института Министерства здравоохранения СССР и кафедра кожных и венерических болезней (зав.— проф. А. А. Антоньев) Центрального института усовершенствования врачей, Москва

С появлением пенициллина и затем других антибиотиков сульфаниламидным соединениям была отведена второстепенная роль. Введение пенициллина в арсенал противогонорейных средств резко сократило сроки лечения больных, привело к значительному снижению случаев безуспешного лечения и осложнений у больных гонореей.

Однако широкое и не всегда обоснованное применение антибиотиков привело к появлению и постепенному увеличению числа штаммов гонококков с пониженной чувствительностью к пенициллину и другим антибиотикам [1—5]. Параллельно с этим наблюдается и увеличение случаев неудач при лечении больных гонореей антибиотиками [6—9].

В литературе также все чаще появляются сообщения о многообразных клинических формах лекарственной аллергии вплоть до случаев со смертельным исходом при назначении антибиотиков [10—12].

Полученные в последнее время полусинтетические пенициллины (метициллин, оксациллин, ампициллин и др.) не разрешили полностью проблемы терапии больных с антибиотикоустойчивыми формами гонореи и с непереносимостью к пенициллину, так как они могут вызывать те же аллергические реакции, что и природные пенициллины.

В связи с этим в последнее время внимание многих исследователей привлекают сульфаниламидные соединения. Высказывались предположения [13], что, поскольку сульфаниламиды в течение многих последних лет широко не применяются у больных гонореей, не исключена возможность повышения чувствительности к ним гонококков. Наблюдения показали, что норсульфазол и сульфадимезин малоэффективны при лечении больных гонореей.

Интерес к сульфаниламидным соединениям значительно повысился после получения препаратов пролонгированного действия (сульфапиридазин, сульфапиродаксин, сульфадиметоксин и др.), которые по своей эффективности превосходят прежние сульфаниламиды.

В настоящем сообщении приведены результаты изучения эффективности сульфамонометоксина и сульфадиметоксина в терапии больных гонореей.

Сульфамонометоксин (синонимы: диаметон, DS-36) и сульфадиметоксин (синонимы: мадрибон, сульксин, суперсульфа) относятся к препаратам пролонгированного действия. В СССР синтезированы во Всесоюзном научно-исследовательском химико-фармацевтическом институте (ВНИХФИ). В эксперименте на животных (мыши и кролики) максимальная концентрация сульфамонометоксина в сыворотке крови определялась через 1—4 часа после введения, держалась на высоком уровне в течение 10 часов, после чего снижалась и составляла 50% максимума [14].

Максимальная концентрация сульфадиметоксина в сыворотке крови у людей после однократного введения 1—2 *г* препарата определяется через

3—8 часов; половина принятой дозы (50%) выводится из организма с м
чой через 48—72 часа [15]. В отличие от других сульфаниламидных пр
паратов до 80% сульфадиметоксина находится в моче в виде хорошо рас
воримого глюкуронида, что практически исключает возможность возни
новения кристаллурии [14].

В опытах на мышах сульфамонометоксин и сульфадиметоксин оказ
лись малотоксичными, проявляли высокую химиотерапевтическую акти
ность при инфекциях, вызванных пневмококком, стрептококком, кише
ной, дизентерийной и брюшнотифозной палочками [14—17]. Длительн
введение сульфадиметоксина мышам не оказывало вредного действия
потомство [18].

Лечение сульфамонометоксином и сульфадиметоксином проведено
153 больных (148 мужчин и 5 женщин), страдавших различными форма
гонорейной инфекции. 92 больных лечили в урологическом стационаре
где они находились 12—17 дней и более и выписывались для дальнейше
диспансерного наблюдения только после комбинированной провокаци
и неоднократных отрицательных результатов лабораторного исследовани
на гонококки. Остальные больные получали лечение амбулаторно.

В возрасте до 20 лет было 11 больных, от 21 года до 30 лет — 10
от 31 года до 40 лет — 32 и старше 40 лет — 8 больных.

Инкубационный период продолжительностью 3—4 дня был констати
рован у 70 больных, от 5 до 7 дней — у 46, 10—14 дней — у 26, от 2 н
дель и более — у 5. У 6 человек длительность инкубационного периода у
тановить не удалось. С давностью заболевания до 7 дней было 34 больны
от 8 до 14 дней — 36, от 2 недель до 1 месяца — 52, от 1 до 2 месяцев — 1
и более 2 месяцев — 12.

Таким образом, более чем у половины больных (83) давность заболе
вания была свыше 2 недель. Это объясняется тем, что из 153 больных, к
торым было назначено лечение сульфамонометоксином и сульфадиметокс
ном, 57 ранее безуспешно лечились различными антибиотиками в други
лечебных учреждениях. У 17 из этих больных рецидив гонореи наступи
после лечения препаратами пенициллина (бензилпенициллин, экмоновоцил
лин, бициллин-3), у 11 — пенициллина и левомицетина, у 5 — пеницил
лина и тетрациклина, у 4 — бициллина-3, мономицина и эритромицина
у 3 — бициллина и мономицина, у 3 — бициллина и эритромицина, у 3 —
бициллина, мономицина и тетрациклина, у 5 — пенициллина и норсуль
фазола, у 2 — тетрациклина, у 2 — метициллина, у 1 — левомицетин
и у 1 больного после последовательного применения экмоновоциллина, ле
вомицетина, олеандомицина, стрептоцида, норсульфазола и тетрациклина.

У всех больных до лечения сульфамонометоксином и сульфадиметок
сином диагноз гонореи был подтвержден лабораторными данными.

При клиническом обследовании у 60 мужчин был диагностирован остры
и подострый передний уретрит, у 59 — острый тотальный уретрит, у 11 —
тотальный уретрит и простатит, у 7 — тотальный уретрит и эпидидимит
у 2 — свежий передний торпидный уретрит и у 8 — хронический уретрит
У 3 женщин была хроническая гонорея и у 2 — острая гонорея нижнег
отдела.

Смешанная гонорейно-трихомонадная инфекция наблюдалась у 12 боль
ных (10 мужчин и 2 женщины).

У 12 больных лечение сульфаниламидными препаратами проведен
в связи с непереносимостью антибиотиков.

Сульфамонометоксин и сульфадиметоксин назначали внутрь в вид
таблеток по 500 *мг*. Больные с неосложненными формами гонореи получал
препарат в курсовой дозе 14—17 *г* (первые 2 дня по 1,5 *г* через каждые 8 ча
сов и последующие дни по 1 *г* 3 раза в сутки); лицам с осложненной, све
жей, торпидной и хронической формами гонореи курсовую дозу увеличива
ли до 20—21 *г*. Больным с торпидной и хронической формами гонореи, кром
сульфаниламидов, назначали иммунотерапию (гоновакцина). Местное ле

чение уретры во время приема препаратов не проводили. В дни приема сульфамонометоксина и сульфадиметоксина назначали обильное щелочное питье (содовая вода, боржоми).

Больным, у которых уретрит сопровождался эпидидимитом или простатитом, для более быстрого разрешения воспалительного инфильтрата в пораженном органе одновременно с сульфаниламидами назначали аутоиммунотерапию, инъекции пирогенала, физиотерапевтические процедуры и др.

Лечение сульфамонометоксином проведено у 69 больных (64 мужчинам и 5 женщинам), при этом 35 из них препарат был назначен после безуспешного лечения различными антибиотиками и 7 — в связи с указанием на непереносимость антибиотиков. Под влиянием терапии сульфамонометоксином гонококки из отделяемого половых органов исчезли у 66 больных (в том числе у всех 35 больных, ранее безуспешно леченных различными антибиотиками). У 3 мужчин клинические симптомы заболевания (обильные выделения из уретры, диффузно мутная моча) продолжали оставаться без изменений на протяжении всего курса лечения, а при микроскопическом обследовании обнаруживались гонококки.

Сульфадиметоксин был применен у 84 мужчин, страдавших различными формами гонореи. Непосредственно после окончания терапии гонококки исчезли из отделяемого уретры у 72 больных (в том числе у 15 из 22 ранее безуспешно леченных антибиотиками). У 12 больных лечение сульфадиметоксином было безрезультатным.

Все больные после окончания лечения находились под нашим наблюдением в течение 1—8 месяцев. В этот период они подвергались неоднократным повторным клиническим и лабораторным обследованиям. Среди больных, леченных сульфамонометоксином, рецидив гонореи был установлен у 5 мужчин (у 4 больных острым уретритом через 5—11 дней после окончания терапии и у 1 больного, ранее безуспешно леченного пенициллином, через $1^1/_2$ месяца).

После терапии сульфадиметоксином ранние рецидивы заболевания были констатированы у 9 человек (в том числе у 2 ранее леченных антибиотиками).

Таким образом, стойкое этиологическое излечение (исчезновение гонококков) наступило у 61 (88,4 %) больного после терапии сульфамонометоксином (при этом у 33 из 35 безуспешно леченных антибиотиками) и у 63 (75 %) больных после назначения сульфадиметоксина (в том числе у 13 из 22 с антибиотикоустойчивыми формами гонореи).

Для изучения быстроты исчезновения гонококков под влиянием терапии сульфаниламидными препаратами продленного действия нами были проведены бактериоскопические исследования отделяемого уретры у 24 больных, леченных сульфамонометоксином и у 15 больных во время терапии сульфадиметоксином. При исследовании почасовых мазков, окрашенных по Граму, установлено, что гонококки из отделяемого уретры исчезали в течение от 8 до 48 часов после начала лечения, причем у большинства из них (36 человек) — через 16—40 часов. Заметной разницы в сроках исчезновения гонококков у больных, успешно леченных сульфамонометоксином и сульфадиметоксином, не наблюдалось.

Постгонорейные воспалительные процессы имелись у 11 больных (9 мужчин и 2 женщины), получавших лечение сульфамонометоксином, и у 16 после терапии сульфадиметоксином. У 6 из них были обнаружены влагалищные трихомонады. У 11 мужчин при уретроскопии были выявлены инфильтративные изменения в слизистой оболочке мочеиспускательного канала и у 10 — простатит.

Лечение сульфамонометоксином и сульфадиметоксином больные переносили хорошо, побочных явлений не наблюдалось. Лишь один больной во время приема сульфамонометоксина жаловался на небольшую головную боль.

Для выяснения возможного влияния препаратов на некоторые функции организма мы изучали в динамике состояние периферической крови, пигментную функцию печени и состав мочи. Исследование морфологического состава периферической крови и содержания билирубина в сыворотке крови проводили до лечения и спустя 7—10 дней после его окончания. Мочу, кроме того, исследовали во время приема препаратов. При этом отклонений от физиологической нормы не наблюдалось.

Таким образом, результаты наших исследований позволяют нам сделать вывод, что сульфамонометоксин является эффективным средством в терапии больных гонореей. Для излечения заболевания достаточно назначения его в курсовой дозе 14—17 *г* больным с неосложненными формами гонореи и в дозе 20—21 *г* при наличии осложнения со стороны придаточных половых желез, а также при торпидных и хронических формах.

Особая ценность сульфамонометоксина состоит в том, что он с успехом может быть применен у больных, которым назначение антибиотиков противопоказано.

Учитывая, что сульфадиметоксин значительно менее эффективен у больных гонореей, чем сульфамонометоксин, а также бо́льшую вероятность возникновения побочных реакций, к его назначению следует прибегать лишь в исключительных случаях.

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Поступила 6.IX 1972 г.

COMPARATIVE EVALUATION OF THERAPEUTIC EFFICACY OF SULPHAMONOMETOXIN AND SULPHADIMETOXIN IN PATIENTS WITH GONORRHEA

F. V. Potapnev, A. A. Skuratovich

Central Research Skin and Venerological Institute of the USSR Ministry of Public Health and Central Post-Graduate Medical Institute, Moscow

Data on the treatment of 84 and 69 patients suffering from gonorrhea with sulphadimetoxin and sulphamonometoxin respectively are presented. Sulphamonometoxin was more effective than sulphadimetoxin. Sulphamonometoxin was especially active in gonorrhea cases previosly treated without any success by various antibiotics.

A. INGREDIENT NAME:

TINIDAZOLE

B. Chemical Name:

1-(2-ethylsuphonylethyl)-2-methyl-5-nitroimidazole

C. Common Name:

Fasigin

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.36% dry basis

E. Information about how the ingredient is supplied:

An almost white or pale yellow, crystalline powder, odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

British Pharmacopeia 1993

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Ripa, T. The plasma half-life was about 13 hours. *Chemotheraapy, Basle,* 1977; 14: 1084.

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Wüst, J. Figures achieved with metronidazole and ornidazole. *Antimicrob, Ag Chemother.* 1977; 11: 631.

Wise, R. The median minimum inhibitory concentration of tinidazole against Bacteroides. *Chemotherapy, Basle,* 1977; 23: 19.

Klastersky, J. The activities of clindamycin, tinidazole, an doxycycline in vitro. *Antimicrob. Ag. Chemother.*, 1977; 12: 563.

Bakshi, J. S. Amoebiasis. *Drugs,* 1978; 15(Suppl): 1, 33.

Apte, V. V. and Packard, R. S. Excellent response was achieved in patients with trichomonal vaginitis. *Drugs,* 1978; 15(Suppl 1): 43.

Welch, J. S. A single doe of tinidazole was as effective as the longer regimen. *Med J Aust.*, 1978; 1: 469.

Levi, G. C. A cure-rate in patients with giardiasis treated with tinidazole. *Am J trop Med. Hyg.* 1977; 26: 564.

Anjaneyulu, R. Trichomoniasis. *J int. med Res.*, 1977; 5: 438.

H. Information about dosage forms used:

Capsules

I. Information about strength:

150mg twice a day

J. Information about route of administration:

Orally

K. Stability data:

Manufacture Date: June 1997
Expiration Date: June 2002
Store in a well-closed container, protected from light.

L. Formulations:

M. Miscellaneous Information:

30-2391
54235

ANALYSIS CERTIFICATE No. 3203

Your Ord. No. - 8th October 1997 Our Ref. No. 2905

MATERIAL TINIDAZOLE JP 12 1-/2-(ethylsulfonyl)-ethyl/-2-methyl-5-nitroimidazole	Quantity	Batch
	Kg. 10.-	75179

Empirical formula	$C_8H_{13}N_2O_4S$	Specific rotation	
Molecular weight	247.28		
Aspect	crystalline powder	Light absorption	
Color	creamish		
Odor	characteristic odour	Loss on drying	0.2565%
Taste		Residue on ignition	0.046%
Melting point	126.1°C	Chloride	
Boiling range		Sulfate	
Solubility	conforms	Heavy metals	max. 10 ppm
		Identification :	positive.
pH			

Titer (Assay) 99.36% dry basis D ✓

Other requirements, notes Related substances by TLC : passes.

Bulk density : 0.6502 gm/u

MANUF. DATE : JUNE 1997
EXPIRY DATE : JUNE 2002 PK

The Analyst

11/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: TINIDAZOLE

MANUFACTURE LOT NO.: 77405

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
PALE YELLOW FINE CRYSTALLINE POWDER; ODORLESS.

2) SOLUBILITY.:
SPARINGLY SOLUBLE IN WATER AND IN ALCOHOL; SOLUBLE IN DILUTE ACIDS.

3) MELTING POINT.:
MELTS AT ABOUT 126-127 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES (A) AS PER IR SPECTRUM CO.SPECS.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

POSSIBLE MUTAGEN.
FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.
---------- PHYSICAL DATA ----------
MELTING PT: 127-128'C
SOLUBILITY: CHLOROFORM-SOLUBLE
APPEARANCE AND ODOR
SOLID.
---------- FIRE AND EXPLOSION HAZARD DATA ----------
EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
---------- REACTIVITY DATA ----------
STABILITY
STABLE.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,
AND NITROGEN OXIDES.
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

NIOSH/MSHA-APPROVED RESPIRATOR.

USE ONLY IN A CHEMICAL FUME HOOD.

COMPATIBLE CHEMICAL-RESISTANT GLOVES.

CHEMICAL SAFETY GOGGLES.

HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

POSSIBLE RISK OF IRREVERSIBLE EFFECTS.

WEAR SUITABLE PROTECTIVE CLOTHING.

DO NOT BREATHE DUST.

POSSIBLE CARCINOGEN.

POSSIBLE MUTAGEN.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE

ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE

HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE

ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL

TERMS AND CONDITIONS OF SALE

---------- IDENTIFICATION ----------

PRODUCT #: T3021 NAME: TINIDAZOLE

CAS #: 19387-91-8

MF: C8H13N3O4S1

SYNONYMS

BIOSHIK * CP 12574 * 1-(2-(ETHYLSULFONYL)-ETHYL)-2-METHYL-5-NITROIMIDAZOLE * FASIGIN * FASIGYN * 1H-IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO- * PLETIL * SIMPLOTAN * SORQUETAN * TINIDAZOL * TINIDAZOLE * TRICOLAM * TRIMONASE *

---------- TOXICITY HAZARDS ----------

RTECS NO: NI6255000

IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO-

TOXICITY DATA

ORL-RAT LD50:2710 MG/KG	IYKEDH 11,811,80
IPR-RAT LD50:2720 MG/KG	IYKEDH 11,811,80
SCU-RAT LD50:3000 MG/KG	IYKEDH 11,811,80
IVN-RAT LD50:>250 MG/KG	YKYUA6 32,204,81
ORL-MUS LD50:3200 MG/KG	JMCMAR 21,781,78
IPR-MUS LD50:2730 MG/KG	IYKEDH 11,811,80
SCU-MUS LD50:3940 MG/KG	IYKEDH 11,811,80
IVN-MUS LD50:>250 MG/KG	YKYUA6 32,204,81

TARGET ORGAN DATA

BEHAVIORAL (SOMNOLENCE)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

LUNGS, THORAX OR RESPIRATION (CYANOSIS)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

EXPOSURE CAN CAUSE:

GASTROINTESTINAL DISTURBANCES

NAUSEA, HEADACHE AND VOMITING

URTICARIA, FLUSHING, PRURITUS, DYSURIA, CYSTITIS, DRYNESS OF THE MOUTH,

DIZZINESS, VERTIGO, AND VERY RARELY, INCOORDINATION AND ATAXIA,

A METALLIC, SHARP, UNPLEASANT TASTE, FURRY TONGUE, GLOSSITIS, AND STOMATITIS.

EXPOSURE TO AND/OR CONSUMPTION OF ALCOHOL

MAY INCREASE TOXIC EFFECTS.

CHRONIC EFFECTS

POSSIBLE CARCINOGEN.

POSSIBLE MUTAGEN.
FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

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SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.
---------- PHYSICAL DATA ----------
MELTING PT: 127-128'C
SOLUBILITY: CHLOROFORM-SOLUBLE
APPEARANCE AND ODOR
SOLID.
---------- FIRE AND EXPLOSION HAZARD DATA ----------
EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
---------- REACTIVITY DATA ----------
STABILITY
STABLE.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,
AND NITROGEN OXIDES.
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

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DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

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USE ONLY IN A CHEMICAL FUME HOOD.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.
CHEMICAL SAFETY GOGGLES.
HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

POSSIBLE RISK OF IRREVERSIBLE EFFECTS.
WEAR SUITABLE PROTECTIVE CLOTHING.
DO NOT BREATHE DUST.
POSSIBLE CARCINOGEN.
POSSIBLE MUTAGEN.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
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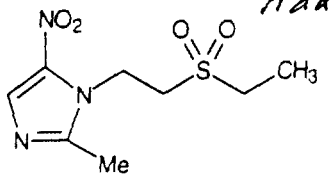
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

Tinidazole ☆



$C_8H_{13}N_3O_4S$ 247.3 *19387-91-8*

Definition Tinidazole contains not less than 98.0% and not more than 101.0% of 1-(2-ethylsulphonylethyl)-2-methyl-5-nitroimidazole, $C_8H_{13}N_2O_4S$, calculated with reference to the dried substance.

Characteristics An almost white or pale yellow, crystalline powder; practically insoluble in *water*; soluble in *acetone* and in *dichloromethane*; sparingly soluble in *methanol*.

Identification *Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.*

A. *Melting point*, 125° to 128°, Appendix V A, Method I.

B. Dissolve 10 mg in *methanol* and dilute to 100 ml with the same solvent. Dilute 1 ml of the solution to 10 ml with *methanol*. Examined between 220 nm and 350 nm, Appendix II B, the solution shows an absorption maximum at 310 nm. The *specific absorbance* at the maximum is 340 to 360.

C. Examine by *infrared absorption spectrophotometry*, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with *tinidazole EPCRS*. Examine the substances prepared as discs.

D. Examine the chromatograms obtained in the test for Related substances. The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of *zinc powder*, 0.3 ml of *hydrochloric acid* and 1 ml of *water*. Heat in a water bath for 5 minutes and cool. The solution yields the reaction characteristic of *primary aromatic amines*, Appendix VI.

Appearance of solution Dissolve 1.0 g in *acetone* and dilute to 20 ml with the same solvent. The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* Y_5, Appendix IV B, Method II.

Related substances Examine by *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance.

Solution (1) Dissolve 0.20 g of the substance being examined in *methanol* with the aid of ultrasound and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with *methanol*.

Solution (3) Dissolve 20 mg of *tinidazole EPCRS* in *methanol* and dilute to 10 ml with the same solvent.

Solution (4) Dilute 1 ml of solution (2) to 20 ml with *methanol*.

Solution (5) Dilute 4 ml of solution (4) to 10 ml with *methanol*.

Solution (6) Dissolve 10 mg of *2-methyl-5-nitroimidazole* (tinidazole impurity A) in *methanol* and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of *tinidazole impurity B EPCRS* in *methanol* and dilute to 100 ml with the same solvent.

Heat the plate at 110° for 1 hour and allow to cool.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of *butan-1-ol* and 75 volumes of *ethyl acetate*. Allow the plate to dry in air and examine in *ultraviolet light (254 nm)*.

Any spots corresponding to tinidazole impurity A and to tinidazole impurity B in the chromatogram obtained with solution (1) are not more intense than the corresponding spots in the chromatogram obtained with solutions (6) and (7), respectively (0.5%).

Any other *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram obtained with solution (5) (0.2%).

Heavy metals 1.0 g complies with *limit test D for heavy metals*, Appendix VII (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb)*.

Loss on drying Not more than 0.5%, determined on 1 g by drying in an oven at 100° to 105°, Appendix IX D.

Sulphated ash Not more than 0.1% determined on 1 g, Appendix IX A, Method II.

Assay Dissolve 0.15 g in 25 ml of *anhydrous acetic acid*. Titrate with 0.1M *perchloric acid VS*, determining the end point potentiometrically, Appendix VIII B. Each ml of 0.1M *perchloric acid VS* is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

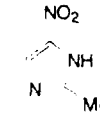
Storage Store in a well-closed container, protected from light.

Action and use Antiprotozoan; antibacterial.

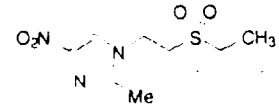
1/96

The impurities limited by the requirements of this monograph include:

2-methyl-5-nitro-1*H*-imidazole *(tinidazole impurity A)*



1-(2-ethylsulphonylethyl)-2-methyl-4-nitroimidazole *(tinidazole impurity B)*



suramin had differing toxicity. Storage in the tropics probably also affected the potency.— E. Nnochiri, *Trans. R. Soc. trop. Med. Hyg.*, 1964, *58*, 413.

Adverse Effects. Suramin may cause nausea, vomiting, abdominal pain, diarrhoea, urticaria, collapse, paraesthesia, hyperaesthesia of the hands and soles of the feet, peripheral neuritis, fever, skin rash, dermatitis, photophobia, lachrymation, amblyopia, and uveitis. A serious effect is albuminuria, with the passage of casts and blood cells. Agranulocytosis and haemolytic anaemia are rare.

When used in onchocerciasis some of the effects may represent an allergic reaction to the killed filariae.

References: Second Report of a WHO Expert Committee on Onchocerciasis, *Tech. Rep. Ser. Wld Hlth Org. No. 335*, 1966.

Pregnancy and the neonate. Suramin had teratogenic effects in *mice*.— H. Tuchmann-Duplessis and L. Mercier-Parot, *C.r. Séanc. Soc. Biol.*, 1973, *167*, 1717, per *Trop. Dis. Bull.*, 1974, *71*, 1107. A woman with advanced trypanosomiasis was successfully treated with suramin and melarsoprol, in addition to supportive therapy, from the 20th week of pregnancy; she gave birth to an apparently normal child.— M. N. Lowenthal, *Med. J. Zambia*, 1971, *5*, 175, per *Trop. Dis. Bull.*, 1972, *69*, 495.

Precautions. It should not be used in the presence of renal disease or adrenal insufficiency.

Absorption and Fate. Following intravenous injection, suramin becomes bound to plasma proteins and a low concentration in plasma is maintained for up to 3 months.

Uses. Suramin is used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma rhodesiense* infections, but as it does not reach the cerebrospinal fluid it is ineffective in the advanced disease when the central nervous system is affected.

Suramin is administered by intravenous injection. To test the patient's tolerance, it is advisable to begin treatment with an injection of 200 mg followed, if well tolerated after 24 to 48 hours by a dose of 20 mg per kg body-weight (up to 1 g) on days 1, 3, 8, 15, and 22. The urine should be tested before each dose, and if protein is present the dose should be reduced or administration delayed.

Combined therapy with tryparsamide has been used, particularly for late *T. gambiense* infection; 12 injections can be given intravenously at intervals of 5 days, each containing suramin up to 10 mg per kg body-weight (max. of 500 mg) and tryparsamide up to 30 mg per kg (max. of 1.5 g), as a 20% solution prepared immediately before use. Two or 3 such courses have been given at intervals of 1 month. Suramin is more commonly used in conjunction with melarsoprol.

Suramin has also been used in the prophylaxis of trypanosomiasis, in a dose of 1 g to provide protection for up to 3 months, but it may mask latent infections. As with pentamidine, it is important to detect more advanced infections and to treat these with melarsoprol.

Suramin is also effective in clearing the adult filariae of onchocerciasis but has only a limited action on microfilariae. The usual dose is 1 g (after an initial test dose) weekly for 5 or 6 weeks. Diethylcarbamazine is active on the microfilariae and the 2 drugs are sometimes used in conjunction.

Onchocerciasis. Less ocular deterioration was observed in a group of patients with onchocerciasis who had been treated 14 to 15 years earlier with a single full course of suramin 4.2 g, than was seen in a similar untreated group.— F. H. Budden, *Trans. R. Soc. trop. Med. Hyg.*, 1976, *70*, 484. The incidence of optic atrophy increased from 1 in 25 to 5 in 25 three years after patients had been treated with suramin 5.2 g (total dose) for ocular onchocerciasis. There was no change in the incidence (1 in 23) in 23 patients not given suramin.— B. Taylefors and A. Rolland, *Bull. Wld Hlth Org.*, 1979, *57*, 479.

For discussions of the treatment of onchocerciasis.— *Br. J. Ophthal.*, 1978, *62*, 427; B. Thylefors, *Bull. Wld Hlth Org.*, 1978, *56*, 63.

Further references: B. O. L. Duke *et al.*, *Tropenmed. Parasit.*, 1976, *27*, 133; J. Anderson *et al.*, *Tropenmed. Parasit.*, 1976, *27*, 263; J. Anderson *et al.*, *Tropenmed Parasit.*, 1976, *27*, 279.

Trypanosomiasis. See Report of a Joint WHO Expert Committee and FAO Expert Consultation, *Tech. Rep. Ser. Wld Hlth Org. No. 635*, 1979.

Preparations

Suramin Injection *(B.P.C. 1973).* A sterile solution of suramin in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections. Store the sealed container in a cool place. Protect from light.

Proprietary Names

Germanin *(Bayer, Ger.)*; Moranyl *(Specia, Fr.)*.

4798-p

Teclozan. Win 13,146. *NN'-p*-Phenylenedimethylenebis[2,2-dichloro-*N*-(2-ethoxyethyl)acetamide].

$C_{20}H_{28}Cl_4N_2O_4 = 502.3$.

CAS — 5560-78-1.

White crystals. M.p. about 142°. Slightly soluble in water.

Adverse Effects. Headache, nausea, vomiting, diarrhoea, and constipation have been reported, but teclozan is generally well tolerated.

Uses. Teclozan is used in the treatment of intestinal amoebiasis. About 20% of a dose is stated to be absorbed and to be rapidly excreted. The usual dose is 100 mg thrice daily for 5 days, or 500 mg daily, in divided doses, for 3 days.

Of 51 patients with chronic intestinal amoebiasis given teclozan 750 mg daily in divided doses after meals for 2 days, 43 were reported to be cured; a further 5 patients responded to a second course of treatment with teclozan. The drug was well tolerated.— D. Huggins, *Anais Esc. nac. Saúde públ. Med. trop.*, 1971, *5*, 29, per *Trop. Dis. Bull.*, 1972, *69*, 399.

Of 30 patients with mild amoebiasis, 25 were reported cured after receiving teclozan 100 mg thrice daily for 5 days; 2 patients required a second course of treatment and 3 remained resistant to teclozan. Two patients developed diarrhoea during treatment which was otherwise well tolerated.— A. Arcilla-Latonio *et al.*, *J. Philipp. med. Ass.*, 1972, *48*, 137, per *Trop. Dis. Bull.*, 1973, *70*, 345.

A cure-rate of 92.8% (at 4 weeks) was achieved in 28 boys with chronic amoebiasis given teclozan 100 mg thrice daily for 5 days.— A. Z. El-Abdin *et al.*, *J. Egypt. med. Ass.*, 1973, *56*, 174, per *Trop. Dis. Bull.*, 1974, *71*, 1028.

Cure in 56 of 60 patients with intestinal amoebiasis after treatment with teclozan 1.5 g in 3 divided doses in 24 hours.— P. Fernandes *et al.*, *Folha med.*, 1974, *69*, 293.

Cure in 26 of 27 children, aged 1 to 5 years, with amoebiasis (usually chronic) after treatment with teclozan 750 mg in 3 divided doses in 24 hours.— H. F. Bezerra *et al.*, *Revta bras. Med.*, 1977, *34*, *Suppl.* (Aug.), 50.

Proprietary Names

Falmonox *(Winthrop, Arg.; Winthrop, USA)*.

4799-s

Tinidazole. CP 12574. 1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole.

$C_8H_{13}N_3O_4S = 247.3$.

CAS — 19387-91-8.

Colourless crystals. M.p. about 127°.

Adverse Effects and Precautions. As for Metronidazole, p.968.

Absorption and Fate. Tinidazole is absorbed from the gastro-intestinal tract.

Pharmacokinetics of tinidazole and metronidazole in man and in *mice*.— J. A. Taylor *et al.*, *Antimicrob. Ag. Chemother.*, 1969, 267.

The biological half-life of tinidazole was 12.7 hours after administration of 150 mg as a single dose and when administered twice daily for 7 days to 7 volunteers. The maximum serum concentration was 8.91 µg per ml.— P. G. Welling and A. M. Monro, *Arzneimittel-Forsch.*, 1972, *22*, 2128. See also B. A. Wood and A. M. Monro, *Br. J. vener. Dis.*, 1975, *51*, 51, per *Abstr. Hyg.*, 1975, *50*, 382.

The peak serum concentrations of tinidazole in 4 volunteers 6 to 11 hours after a single dose of 2 g were between 20 and 40 µg per ml, and 48 hours after ingestion the serum concentration was still above the minima. trichomonacidal concentration for most of the 8 strains of *Trichomonas vaginalis* examined.— A. Forsgren and J. Wallin, *Br. J. vener. Dis.*, 1974, *50*, 146 and 148, per *Abstr. Hyg.*, 1974, *49*, 593.

In 6 gynaecological patients given a single dose of tinidazole 2 g peak serum concentrations were 32 to 52 µg per ml 3 to 6 hours after the dose, and 18 to 35 µg per ml 8.5 to 15 hours after the dose. Concentrations in saliva, vaginal secretions, peritoneal fluid, and various tissue homogenates were broadly comparable with those in serum. The plasma half-life was about 13 hours.— T. Ripa *et al.*, *Chemotherapy, Basle*, 1977, *23*, 227, per *Int. pharm. Abstr.*, 1977, *14*, 1084.

In 4 healthy subjects given tinidazole 2 g concentrations in the CSF 90 minutes later (17 to 39 µg per ml) were 88% of those in serum.— A. M. M. Jokipii *et al.*, *J. antimicrob. Chemother.*, 1977, *3*, 239.

Uses. Tinidazole which is a nitroimidazole like metronidazole has antiprotozoal activity and is effective against *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Giardia lamblia*. It is also active against anaerobic bacteria.

In trichomoniasis it is given by mouth in a dose of 150 mg twice daily for 7 days or as a single dose of 2 g to both men and women. It has been given in similar doses in the treatment of giardiasis.

In amoebiasis doses of 2 g once daily for 3 days are commonly used.

A review of tinidazole in the treatment of trichomoniasis, amoebiasis, and giardiasis.— P. R. Sawyer *et al.*, *Drugs*, 1976, *11*, 423.

Proceedings of a symposium on the use of tinidazole in the treatment of amoebiasis, giardiasis, and trichomoniasis.— *Drugs*, 1978, *15*, *Suppl.* 1, 1–60.

The following anaerobic bacteria were inhibited by 3.1 µg per ml of tinidazole and killed by 6.3 µg per ml: *Bacteroides fragilis* and *melaninogenicus*, *Clostridium perfringens* and other species of clostridia, *Eubacterium*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, and *Veillonella* spp. *Propionibacterium acnes* was relatively resistant. The same figures were achieved with metronidazole and ornidazole.— J. Wüst, *Antimicrob. Ag. Chemother.*, 1977, *11*, 631.

The median minimum inhibitory concentration of tinidazole against *Bacteroides* spp. was 0.12 µg per ml compared with 0.25 µg per ml for metronidazole or nimorazole.— R. Wise *et al.*, *Chemotherapy, Basle*, 1977, *23*, 19.

The activities of clindamycin, tinidazole, and doxycycline *in vitro* were compared against 376 anaerobic bacteria. Clindamycin and tinidazole had MICs of 0.5 and 3 µg per ml respectively against 90% of 200 strains of *Bacteroides fragilis*. Tinidazole had an MIC of 12 µg per ml against 72 strains of the *Clostridium* spp. but benzylpenicillin and ampicillin were more active. Tinidazole was generally less active than benzylpenicillin, ampicillin, cephalothin, carbenicillin, erythromycin, chloramphenicol, tetracycline, and doxycycline against 20 strains of *Bacteroides melaninogenicus*, 54 of the *Fusobacterium* spp., and 30 strains of anaerobic Gram-positive cocci.— J. Klastersky *et al.*, *Antimicrob. Ag. Chemother.*, 1977, *12*, 563.

Amoebiasis. In a series of controlled studies 436 patients with intestinal amoebiasis were treated with tinidazole 600 mg twice daily for 5 days or 2 g once daily for 3 days, or metronidazole 400 mg thrice daily for 5 days or 2 g once daily for 3 days. Cure-rates for tinidazole were 97.2% and 88.3% respectively in patients passing trophozoites and 81.2% and 93.4% in those passing cysts, compared with 87.5% and 73.3%, and 84.2% and 47.3% for metronidazole. A cure-rate of 96% was achieved in 51 patients with hepatic amoebiasis given tinidazole 2 g once daily for 2 days, compared with 75.5% in 49 given metronidazole. A cure-rate of 88.3% was achieved in 94 patients with giardiasis given tinidazole in a mean dose of 61.8 mg per kg as a single dose, compared with 46.7% in 92 given metronidazole 56 mg per kg.— J. S. Bakshi *et al.*, *Drugs*, 1978, *15*, *Suppl* 1, 33.

In a multicentre study in 8 countries a cure-rate of 95% was achieved in 502 patients with amoebiasis given tinidazole 2 g once daily (50 mg per kg body-weight for children) for 2 or 3 days. An excellent response was achieved in 60, and a good response in 17, of 82 with hepatic amoebiasis. A cure-rate of 88% was achieved in 3 children with giardiasis given a single dose of about 50 mg per kg. A cure-rate of 95.2% was achieved in 859 patients with trichomonal vaginitis given a single dose of 2 g.— V. V. Apte and R. S. Packard, *Drugs*, 1978, *15, Suppl.* 1, 43.

Of 88 aboriginal children infected with *Giardia lamblia* or *Entamoeba histolytica* 23 received a single dose of tinidazole 1 to 1.5 g, 23 tinidazole 1 to 1.5 g daily for 3 days, 23 metronidazole 200 mg twice daily for 5 days, and 19 were left untreated. Both metronidazole and tinidazole successfully cleared the majority of *G. lamblia* infections but *E. histolytica* infections were more effectively treated with tinidazole. A single dose of tinidazole was as effective as the longer regimen. No adverse reactions occurred with either drug.— J. S. Welch *et al.*, *Med. J. Aust.*, 1978, *1*, 469.

Further references: N. Islam and M. Hasan, *Curr. ther. Res.*, 1975, *17*, 161; J. N. Scragg *et al.*, *Archs Dis. Childh.*, 1976, *51*, 385.

Liver abscess. Tinidazole 57 mg per kg body-weight daily for 5 days or 50 mg per kg daily for 3 days was effective in the treatment of amoebic liver abscess in 23 of 25 children aged 3 months to 6 years.— J. N. Scragg and E. M. Proctor, *Archs Dis. Childh.*, 1977, *52*, 408.

Of 16 patients with hepatic amoebiasis 15 were cured after treatment with tinidazole 2 g as a single dose daily for 3 to 6 days, compared with 12 of 15 given metronidazole in the same dosage regimen for 4 to 10 days.— N. Islam and K. Hasan, *Drugs*, 1978, *15, Suppl.* 1, 26.

Further references.— H. A. Meyer, *E. Afr. med. J.*, 1974, *51*, 923, per *Trop. Dis. Bull.*, 1975, *72*, 720; S. N. Mathur *et al.*, *J. int. med. Res.*, 1977, *5*, 429; M. A. Quaderi *et al.*, *J. trop. Med. Hyg.*, 1978, *81*, 16.

Giardiasis. Cure in 35 of 38 children with giardiasis after a single dose of tinidazole; 2 others were cured after a second dose. Doses were: under 1 year, 500 mg; 7 years, 1 g; 12 years, 1.5 g.— S. Danzig and W. L. F. Hatchuel (letter), *S. Afr. med. J.*, 1977, *52*, 708, per *Trop. Dis. Bull.*, 1978, *75*, 783.

A cure-rate of 96.7% in patients with giardiasis treated with tinidazole 150 mg twice daily for 7 days.— G. C. Ravi *et al.*, *Am. J. trop. Med. Hyg.*, 1977, *26*, 564, per *Trop. Dis. Bull.*, 1978, *75*, 648. See also S. Y. Salih and R. E. Abdalla, *J. trop. Med. Hyg.*, 1977, *80*, 11, per *Trop. Dis. Bull.*, 1977, *74*, 731.

Cure of 53 of 55 patients with giardiasis given tinidazole 2 g as a single dose.— N. A. El Masry *et al.*, *Am. J. trop. Med. Hyg.*, 1978, *27*, 201, per *Trop. Dis. Bull.*, 1978, *75*, 544.

See also under Amoebiasis, above.

Further references: L. Jokipii and A. M. M. Jokipii, *J. infect. Dis.*, 1979, *140*, 984; M. B. Tadros, *J. Egypt. Soc. Parasit.*, 1979, *9*, 467, per *Trop. Dis. Bull.*, 1980, *77*, 125; A. Sabchareon *et al.*, *S.E. Asian J. trop. med. publ. Hlth*, 1980, *11*, 280, per *Trop. Dis. Bull.*, 1981, *78*, 161.

Prophylaxis in surgery. In a prospective, randomised, double-blind study of 6 months' duration involving 71 patients 2 g of tinidazole given before surgery prevented wound infection after elective colonic surgery in 37 of 40 patients in comparison with 28 of 31 patients treated with placebo.— P. S. Hunt *et al.*, *Med. J. Aust.*, 1979, *1*, 107.

Postoperative infections occurred in 6 of 50 patients who received 2 g of tinidazole 12 to 18 hours before undergoing elective abdominal hysterectomy and 2 g 48 hours postoperatively; infections occurred in 28 of 50 similar control patients.— P. C. Appelbaum *et al.*, *Chemotherapy, Basle*, 1980, *26*, 145.

Further references: J. Adno and R. Cassel, *S. Afr. med. J.*, 1979, *56*, 565 (gynaecological surgery); M. Karhunen *et al.*, *Br. J. Obstet. Gynaec.*, 1980, *87*, 70 (hysterectomy).

Trichomoniasis. Tinidazole 2 g as a single dose produced parasitological cure in 47 of 50 patients with trichomoniasis, compared with 32 of 50 given metronidazole.— R. Anjaneyulu *et al.*, *J. int. med. Res.*, 1977, *5*, 438.

Further reports of the successful use of 2-g doses of tinidazole in women.— H. T. M. Rao and D. R. Shenoy, *J. int. med. Res.*, 1978, *6*, 46; J. P. Ward, *Med. J. Aust.*, 1976, *2*, 651; R. Jones and P. Enders, *ibid.*, 1977, *2*, 679; M. Massa *et al.*, *Boln chil. Parasit.*, 1976, *31*, 46, per *Trop. Dis. Bull.*, 1977, *74*, 291.

Successful use in men of single 1-g doses of tinidazole.— N. Kawamura, *Br. J. vener. Dis.*, 1978, *54*, 81, per *Abstr. Hyg.*, 1978, *53*, 465.

See also under Amoebiasis, above.

Vaginitis. Administration of a single dose of tinidazole 2 g to 35 women with *Gardnerella vaginalis (Haemophilus vaginalis)* infection led to disappearance of the bacteria in 33; of the other 2 women the count was reduced in one and a repeat treatment was successful in the second. Two women relapsed after 15 to 20 days and repeat treatment was successful. All the patients' partners were given the same dose of tinidazole, and abstinence from sexual intercourse was recommended for at least 24 hours.— M. Bardi *et al.* (letter), *Lancet*, 1980, *1*, 1029.

See also under Trichomoniasis, above.

Proprietary Names

Fasigin *(Pfizer, Ital.)*; Fasigyn *(Pfizer, Arg.; Pfizer, Austral.; Roerig, Belg.; Pfizer, Denm.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.)*; Fasigyne *(Pfizer, Fr.)*; Simplotan *(Pfizer, Ger.)*; Trichogin *(Chiesi, Ital.)*; Tricolam *(Pfizer, Spain)*.

6000-c

Tryparsamide *(B.P. 1968)*. Tryparsam.; Tryparsamidum; Glyphenarsine; Tryparsone. Sodium hydrogen 4-(carbamoylmethylamino)phenylarsonate hemihydrate. $C_8H_{10}AsN_2NaO_4.\frac{1}{2}H_2O = 305.1$.

CAS — 554-72-3 (anhydrous); 6159-29-1 (hemihydrate).

Pharmacopoeias. In *Ind., Int., It., Mex.*, and *Turk.*

A colourless, odourless, crystalline powder which is slowly affected by light.

Soluble 1 in 1.5 of water, forming a neutral solution; soluble 1 in 3500 of alcohol; practically insoluble in chloroform and ether. A 4.62% solution is iso-osmotic with serum. Aqueous solutions deteriorate on storage and should be used immediately after preparation; solutions for injection are prepared aseptically. Store in a cool place in small airtight containers. Protect from light.

Adverse Effects. Side-effects include dizziness, tinnitus, nausea, vomiting, headache, fever, exfoliative dermatitis, allergic reactions, and bradycardia immediately after an injection. Liver damage may also occur.

The most serious toxic effect is upon the optic nerve. Treatment should be discontinued immediately if visual defects appear; though blindness may occur suddenly, especially if optic injury is already present, visual defects may not become apparent until a few weeks after a course of treatment has been completed.

Uses. Tryparsamide is trypanocidal. Because it penetrates the cerebrospinal fluid it has been used in the treatment of African trypanosomiasis with central nervous system involvement particularly in *Trypanosoma gambiense* infections. It has been given in doses of 30 to 60 mg per kg body-weight (up to maximum of 2 g) intravenously each week for 12 to 14 weeks. The trypanosomes may become resistant to tryparsamide. Because of the risk of blindness, melarsoprol is now preferred.

For the use of tryparsamide in conjunction with suramin, see p.984.

Preparations

Tryparsamide Injection *(B.P. 1968)*. Tryparsam. Inj. A sterile solution in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections.

Database: Medline <1995 to February 1998>

<1>
Unique Identifier
96415043
Authors
Salo JP. Salomies H.
Title
High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. II. Hydrolysis kinetics of tinidazole.
Source
Journal of Pharmaceutical & Biomedical Analysis. 14(8-10):1267-70, 1996 Jun.
Abstract
In a citrate-borate-phosphate buffer, 5 mM tinidazole solutions exhibited maximum stability stability around pH 4.0-5.0. The hydrolysis of tinidazole was mostly a first-order reaction. At pH 10.0 and 60-80 degrees C, tinidazole had an activation energy of 122 kJ mol-1 for hydrolysis. It was postulated that tinidazole decomposes by different mechanisms under basic and neutral/acidic conditions.

<2>
Unique Identifier
96415042
Authors
Salo JP. Salomies H.
Title
High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. I. Development and validation method.
Source
Journal of Pharmaceutical & Biomedical Analysis. 14(8-10):1261-6, 1996 Jun.
Abstract
A stability-indicating high performance thin layer chromatography method for analyzing hydrolyzed tinidazole solutions using silica gel plates was developed and validated. The mobile phase used was methanol-diethyl ether-chloroform (1:9:3, v/v/v) allowing small changes in its composition. Detection was at 314 mm. Rf values being 0.1-0.4, baseline resolution was achieved for tinidazole and the hydrolysis products. The analytes were stable on the sorbent and could be precisely and accurately measured

in the range 20-170 ng per band.

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Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate

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Summary

Tinidazole (40 mg/kg body-weight in one daily dose for five days) and tinidazole (same dose) plus diloxanide furoate (20 mg/kg body-weight divided into three daily doses for 10 days) were compared as treatments for amoebiasis. The parasitic cure rates were 44 and 91% respectively. We cannot, therefore, recommend tinidazole alone in this dosage as a treatment for non-invasive amoebiasis.

Introduction

Tinidazole (Fasigyn) has recently been widely used as an alternative to metronidazole for the treatment of infections with *Entamoeba histolytica*. In a previous study (PEHRSON, 1982), tinidazole was given to a series of patients with chronic intestinal or asymptomatic amoebiasis. When checked by at least three stool specimens taken on different days, one month after treatment, we found a parasitic cure rate (p.c.r.) of 0% (0/14). This should be compared with the results obtained in other studies, showing a cure rate of 77 to 96% (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978), using the same dosage schedule but mainly in cases of acute intestinal amoebiasis.

To investigate the reasons for the unsatisfactory response we obtained, which could be due to too low a dose or to a low efficiency of tinidazole in the gut lumen, we carried out a new trial with a higher daily dose of tinidazole and compared the effect of this higher dose with that following treatment with tinidazole and diloxanide furoate (Furamide) in combination. This latter was found to be an effective intraluminal amoebicide (WOODRUFF & BELL, 1960, 1967; WOLFE, 1973), whose mode of action upon the amoeba is unknown. We omitted Furamide as a single regimen, because it is considered to be ineffective against invasive amoebiasis and there is always a risk of developing an invasive form of the disease if zymodeme differentiation of strains of *Entamoeba histolytica* is not performed routinely (SARGEAUNT & WILLIAMS, 1978; SARGEAUNT *et al.*, 1982).

Materials and Methods

During the period of the study, 41 patients were diagnosed as suffering from amoebiasis. All of them were supposed to have contracted their infections abroad, as amoebiasis is not considered to be endemic in Sweden. No cases of acute, dysenteric amoebiasis or diagnosed or suspected cases of liver abscess were included. The patients had not received any anti-amoebic drug during the previous year. Nine of the patients had a concomitant infection with *Giardia lamblia*, two with *Shigella flexneri*, two with *Campylobacter jejuni*, one with *Salmonella paratyphi A*, one with *Hymenolepis nana*, one with *Ascaris lumbricoides* and one with *Trichuris trichiura*.

In a predetermined, random order, the patients were allocated to two groups, 18 being treated with tinidazole alone and 23 with the combination. All were hospital in-patients and kept under supervision during treatment.

Dosage schedules

(1) tinidazole 40 mg/kg body-weight in one daily dose for five days;

(2) tinidazole as above plus diloxanide furoate 20 mg/kg body-weight divided into three daily doses for 10 days.

Approximately one month after the treatment was completed, checks were made, including the examination of at least three stool specimens taken on different days. One of these was examined by direct microscopy of freshly passed, loose faeces induced by a 50% magnesium sulphate purgative and the other normally passed specimens were examined by the formol-ether-concentration technique described by RIDLEY & HAWGOOD (1956). Failure was defined as the persistence of amoebic trophozoites or cysts in any of these specimens.

Those in whom the treatment with tinidazole failed were later treated with the combination of tinidazole and diloxanide furoate and those in whom the combination failed were treated with metronidazole 40 mg/kg body-weight daily for 10 days.

Results

Data on the participants and the results of the checks one month after treatment are shown in Table I. In no case were the side effects severe enought to cause cessation of treatment. Statistical analysis was made, using the chi-square test, and showed a significant difference between the two groups on the 1%-level (two-tailed test) and in favour of the combination. No differences could be found between the response of Swedes and that of the immigrants, or between those infected on different continents (Asia, Africa, South America). The presence of other parasites did not seem to affect the outcome of the treatment.

Discussion

Our results with tinidazole alone (44% p.c.r.), in treating non-dysenteric amoebiasis, are unsatisfactory and differ very much from those obtained in previously published studies by different authors, using the same dosage schedules (77 to 96% p.c.r.) (ISLAM & HASAN, 1975; APTE & PACKARD, 1978) or lower (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKASHI *et al.*, 1978). The patients in these studies were, however, mainly cases of acute amoebic dysentery, a factor which may have influenced the results.

A weak amoebicidal effect of the nitroimidazoles on the cyst stage of *E. histolytica* was observed by

Table I—Some characteristics and treatment results of 41 patients with non-invasive amoebiasis

Treatment	No.	Median age (age range) years	Patients with symptoms v. asymptomatics	Swedes v. other nationalities	Parasite-free at check	Parasite cure rate
Tinidazole 40 mg/kg × 1 + V	18	28 (9-68)	11:7	8:10	8	44%
Tinidazole 40 mg/kg × 1 × V + diloxanide furoate 500 mg × 3 × X	23	26 (6-68)	15:8	11:12	21	92%

SPILLMAN *et al.* (1976), but this report was contradicted by BAKSHI *et al.* (1978). Our drug trial was carried out in a country in which amoebiasis is not endemic, making reinfection during follow-up very unlikely, and confirming that the low p.c.r. was caused by "true" treatment failures.

We therefore believe that our poor results with tinidazole alone are due to its ineffectiveness in eradicating cysts in the lumen of the gut, either because of too effective absorption (MONRO, 1974) or inactivation by aerobic organisms as shown by RALPH & CLARKE (1978).

When tinidazole was combined with diloxanide furoate, we obtained a cure rate of 91%, which may be compared with studies by WOODRUFF & BELL (1967), in which they reported a cure rate of 95% in amoebic cyst-passers treated with diloxanide furoate alone for 10 days and WOLFE (1973), who found a cure rate of 83% using the same schedule. It is also noteworthy that all our failures with tinidazole alone have proved to be freed from their infection after treatment with the combination.

Acknowledgements

We wish to thank Mrs. Inger Pontén, the head nurse in the tropical ward and Birgit Lindberg, the chief technician at the laboratory of tropical diseases, for their devoted work with the patients.

References

Apte, V. V. & Packard, R. S. (1978). Tinidazole in the treatment of trichomoniasis, giardiasis and amoebiasis. Report of a multicentre study. *Drugs*, **15** (Suppl. 1), 43-48.

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